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FLAVONOID COMPOUNDS AS THERAPEUTICS ANTIOXIDANTS

Novel Flavonoid Compounds, their Manufacture and

2	use as Therapeutic Antioxidants.
3	
4	The present invention relates to new analogues of
5	phytochemicals, to compositions comprising these
6.	analogues and to the use of these analogues as
7	therapeutic agents.
8	
9	Particularly but not exclusively the present
10	invention relates to new analogues of flavonoids
11	having improved lipid solubility and the ability to
12	orientate themselves within lipid membranes.
13	
14	Oxidative damage to cells is implicated in the
15	development of many clinical conditions including
16	ischaemia-reperfusion injury, cancers, heart
17	disease, arthritis, neurological disorders and
18	auto-immune diseases. To date preventative therapy
19	with antioxidants has not been very successful,
20	partly because targeting and orientating the
21	compounds at the correct site within the cell for
22	optimum effect is difficult. Evidence is now

below;

1 emerging that effective antioxidant intervention 2 during the acute phase of ischaemic events may 3 increase survival rate and minimise irreversible organ damage. 4 5 6 Combinational therapies for treatment of diseases 7 currently incorporate natural and synthetic antioxidants with limited success. 8 There is a need to produce antioxidant agents that possess low 9 toxicity and high therapeutic benefit for use in 10 pharmaceutical preparations. Current natural 11 flavonoid antioxidants are relatively ineffective, 12 being inefficient at protecting cell membranes from 13 14 free radical oxidative damage. 15 16 The low bioavailability and uptake by the human 17 body of dietary antioxidants is a limiting factor 18 in their therapeutic action. Dietary antioxidants have poor performance in the treatment of diseases 19 such as Parkinson's and Alzheimer's and in 20 21 ameliorating ischaemia-reperfusion injury. 22 . 23 Vitamin E $(d-\alpha-tocopherol)$ is a widely used and 24 naturally occurring antioxidant. It is known to 25 protect cell membranes from free radical mediated 26 oxidative damage. The chemical structure of vitamin E $(d-(2R,4'R,8'R)-\alpha-Tocopherol)$, is shown 27

1

2 The recognised essential dietary antioxidants are

3 vitamin E and vitamin C. There are also a range of

4 metals, including selenium, iron, copper, zinc and

5 manganese, required from the diet to allow the

6 enzymes to function with antioxidant activity.

7 Carotenoids from the diet may also have antioxidant

8 properties in-vivo in the scavenging of singlet

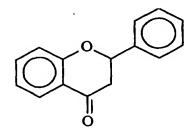
9 oxygen and in tissues of low partial oxygen

10 pressure.

11

12 Alternative natural antioxidants include flavonoids

which have the following general structure:



14

15 Flavonoids are polyhydroxyphenolic products of the

16 phenylpropanoid biosynthetic pathway in plants, and

17 there are more than 4000 naturally-occurring

18 flavonoids. They are present in a wide range of

19 fruits, vegetables, nuts, and beverages including

20 wine and tea. Flavonoids fall into two distinct

21 groups depending on whether the central

22 heterocyclic ring is saturated or unsaturated. If

1 the central heterocyclic ring is unsaturated (as in

2 anthocyanidin, flavones, flavonols), the molecule

3 is achiral. If the central heterocyclic ring is

4 saturated, as shown above, (as in flavanones and

5 flavans), one or more chiral centres are present,

6 and thus such flavonoids exhibit optical activity.

7 A number of flavonoid structures are shown below;

8

9

10

Flavan-3-ol

11

12 Selected flavonoids, such as myricetin, exhibit

13 potent antioxidant properties and are more

14 effective as antioxidants than vitamin E both in

15 terms of the number of radicals which one molecule

16 can reduce and in terms of the rate of the radical

17 annihilation reaction. However, flavonoids are

1	poor membrane protectants due to their limited
2	lipid solubility. Consequently flavonoids have had
3	limited application as antioxidants in vivo.
4	
5	Our kinetic and stoichiometric studies comparing
6	the reducing capabilities of flavonoids to d- $lpha$ -
7	tocopherol indicate that the antioxidant activity
8	is markedly influenced by the number and position
9	of the hydroxyl groups on the B and C rings as well
10	as the extent of conjugation between the B and C
11	rings. Moreover, within a biological system where
12	a number of polyphenols may be present at similar
13	concentrations, antioxidant efficacy may be
14	predominantly governed by reaction kinetics rather
15	than stoichiometry.
16	·
17	The present invention provides novel compounds
18	having both potent antioxidant activity together
19	with high lipid solubility, thus facilitating their
20	sequestration into the cell membrane.
21	
22	According to one aspect of the present invention
23	there is provided a compound of the following
24	Formula 1:
25	

25

6

$$\begin{array}{c|c} R_{10} & R_{11} \\ R_{10} & B \\ R_{13} & C \\ R_{13} & R_{14} \end{array}$$

Formula 1

2 wherein R_A is a C_2 to C_{30} saturated or unsaturated 3 hydrocarbon chain; 4 5 R_{10} , R_{11} , R_{13} , R_{14} and R_{3} each independently 6 represent H, OH, a C1-6 ether, or a saturated 7 or unsaturated hydrocarbon chain which may be 8 substituted with one or more of nitro, 9 halogen, amino, hydroxyl, ketone or aldehyde 10 11 group; 12 optionally there is a double bond between C2 13 and C3 of the C ring; 14 15 n represents 0 or 1; and 16 17 R_8 is a C_2 to C_{15} saturated or unsaturated 18 hydrocarbon chain, and where R_B is present, R_A 19 and R_B are both C_2 to C_{12} aliphatic alkyl 20 21 chains. 22 Preferably at least one of R_{10} , R_{11} and R_{13} 23 represents OH. More preferably at least three of 24

 R_{10} , R_{11} , R_{13} , R_{14} and R_{3} represent OH.

1	Preferably R_{10} and/or R_{11} represent OH.
2	
3	In one embodiment both R_{11} and R_{13} represent OH, and
4	more preferably R_3 , R_{11} and R_{13} all represent OH.
5	
6	Alternatively R_3 and R_{10} both represent OH, more
7	preferably R_3 , R_{10} and R_{13} all represent OH.
8	·
9	Optionally one or more of R_{10} , R_{11} , R_{13} , R_{14} and R_{3}
10	represents an ether, preferably a C_{1-4} ether.
11	
12	Advantageously the flavonoid group is an extended
13	conjugated π -electron system.
14	
15	Preferably there is a double bond between C_2 and C_3
16	of the C ring.
17	
18	Preferably the B and C rings of the flavonoid have
19	the structure of the B and C rings of myricetin,
20	morin, quercetin, kaempferol, luteolin, or
21	apigenin. More preferably the B and C rings of the
22	flavonoid group have the structure of the B and C
23	rings of myricetin.
24	
25	Alternatively the B and C rings of the flavonoid
26	group may have the structure of the B and C rings
27	of taxifolin or catechin.
28	
29	The backbone of R_A may have from two to twenty
30	carbon atoms, preferably from six to fifteen carbon
31	atoms. Suitably the R_A backbone has two, three,
32	four, five, six, seven, eight, nine, ten, eleven,

8

- 1 twelve, thirteen, fourteen, fifteen, sixteen,
- 2 seventeen or eighteen carbon atoms. More
- 3 preferably the RA backbone has eight, nine or ten
- 4 carbon atoms. Optionally the RA backbone comprises
- 5 nine, ten, eleven or twelve carbon atoms in total
- 6 (ie. backbone plus any side chains).

7

- 8 Preferably the backbone of RA has eight, nine or
- 9 ten carbon atoms, and R_3 , R_{11} and R_{13} each represent
- 10 OH.

11

- 12 The backbone of RA and/or RB may be saturated or
- 13 unsaturated. Preferably the backbone is saturated,
- 14 but this is not always essential.

15

- 16 Suitably RA is attached to position 5, 6, 7 or 8 of
- 17 the A ring of the flavonoid group. Preferably RA
- 18 is attached to position 7 of the A ring of the
- 19 flavonoid group.

20

- 21 Suitably R_B is attached to position 5, 6, 7 or 8 of
- 22 the A ring (but R_B may not be attached to the same
- position of the A ring as R_A). Generally R_B is a
- 24 saturated alkyl chain of C₁ to C₆, for example C₁ to
- 25 C4, typically C2 or C3. Usually RB is a straight-
- 26 chained alkyl group.

27

- 28 In a preferred embodiment RA has the following
- 29 structure:

$$H_3C$$
 CH_3
 CH_3
 CH_2
 CH_2

1 wherein

n is an integer from 1 to 7, preferably 2 or

3 3; and

m is an integer from 1 to 7, preferably 1 or

5 2.

6

7 More preferably RA has the following structure:

8

9 Alternatively RA has the following structure:

10

11 wherein n is an integer from 2 to 27, preferably n

12 is 4 to 12, more preferably n is 5 to 7 (ie. giving

13 a total chain length of 8 to 10).

14

15 In another embodiment RA has the following

16 structure:

17

18 wherein

x is an integer from 1 to 25, preferably 1 to

20 15, more preferably x is 1, 2, 3, 4, or 5;

10

y is an integer from 1 to 25, preferably 1 to

15, more preferably y is 1, 2, 3, 4, or 5;

and wherein x + y = 25 or less, preferably x + y = 2, 3, 4 or 5.

6

7 In another embodiment R_A has the following

8 structure:

$$H_3C$$
 CH_3
 CH_2
 CH_2

9

10 wherein

n is an integer from 1 to 7, preferably n is

1, 2, or 3, most preferably n is 1; and

13

m is an integer from 1 to 7, preferably m is

1, 2 or 3, most preferably m is 1.

16

17 In one embodiment, the flavonoid group of the

18 compound of the present invention preferably has

19 the following structure:

20

21

22

23

1 2

3

- 4 In one embodiment, the compound of the present
- 5 invention has the following structure:

6

7

ОН

OH

ОН

12

1

2

3

4

5

6

1 OH OH OH

OH OH OH

OH OH OH

5 Whilst the Applicant does not wish to be bound by

6 theoretical considerations, it is believed that

7 addition of R_A and optionally R_B to the A-ring

8 increases membrane partitioning and also adds the

9 important spatial distribution factor observed with

10 vitamin E. It is anticipated that crossing of the

11 blood/brain barrier will also be enhanced.

12

4

2

1	According to a further aspect of the present
2	invention there is provided a composition
3	comprising a compound as described above and at
4	least one pharmaceutically acceptable excipient or
5	carrier. The composition may be a sunscreen
6	composition.
7	
8	According to a further aspect of the present
9	invention there is provided a method of preventing
10	UV damage to the skin (for example sunburn or skin
11	cancers such as melanoma) of a mammalian animal,
12	said method comprising the step of administering a
13	therapeutically effective amount of the sunscreen
14	composition as described above to a patient's skin
15	prior to UV exposure. The method is of most
16	interest for human patients.
17	
18	The composition will usually be applied topically
19	to the patient's skin.
20	
21	The composition may alternatively be formulated as
22	a skincare composition and may, for example,
23	include emollients and moisturisers. The skincare
24	composition may be of particular utility in
25	preventing or reversing the effects of ageing, of
26	reducing apparent wrinkling, and/or treating or
27	preventing dry skin.
28	
29	According to a further aspect of the present
30	invention there is provided a foodstuff stabiliser
31	composition comprising a compound as described
	-

15

It is believed that the ability to combat free 1 radicals will be of utility in preventing or 2 delaying the deterioration in food quality during 3 It is envisaged that the composition will 4 be particularly effective where the foodstuff 5 stabiliser composition is in the form of an 6 emulsion, especially an emulsion having a low 7 fat/high water content. The foodstuff stabiliser 8 composition will be particularly suitable for low 9 fat spreads, salad dressings etc. 10 11 According to a further aspect of the present 12 invention there is provided a method of treating a 13 patient having a disease or disorder involving 14 oxidative damage, said method comprising the step 15 of administering a therapeutically effective amount 16 of the composition described above to said patient. 17 Generally said patient will be a human, but 18 treatment of other mammalian animals is also 19 possible. The method of the present invention may 20 also be used prophylactically to prevent a patient 21 developing a disease or disorder involving 22 oxidative damage. 23 24 The disease or disorder involving oxidative damage 25 may be selected from the group consisting of cancer 26 (for example colon, liver or bladder cancer), heart 27 disease, especially to prevent subsequent heart 28 attacks, neurological disorders, (particular 29 mention may be made of Alzheimer's or Parkinson's 30 disease), auto-immune disorders (particularly 31 arthritis), ischaemia-reperfusion injury 32

16

(particularly stroke, or risk of stroke), diabetic 1 complications, septic shock, hepatitis, 2 atherosclerosis and complications arising from HIV 3 or Hepatitis B. 4 5 If the disease or disorder is stroke or risk of 6 stroke, the composition described above is 7 preferably administered before the stroke occurs as . 8 a prophylatic to reduce the risk of stroke 9 occurrence, or within twelve hours (preferably 10 within four hours) of stroke occurrence. 11 12 Most suitably the disease or disorder to be treated 13 is an ischaemia-reperfusion injury. 14 15 According to a further aspect of the present 16 invention there is provided the use of a compound 17 of Formula 1 as described above for the manufacture 18 of a medicament for the treatment or prevention of 19 a disease or disorder involving oxidative damage. 20 The disease or disorder may be cancer (for example 21 colon, liver or bladder cancer), heart disease, 22 especially to prevent subsequent heart attacks, 23 neurological disorders, (particular mention may be 24 made of Alzheimer's or Parkinson's disease), auto-25 immune disorders (particularly arthritis), 26 ischaemia-reperfusion injury (particularly stroke 27 or risk of stroke), diabetic complications, septic 28 shock, hepatitis, atherosclerosis, and 29

complications arising from an immune response to

HIV or Hepatitus B. Most suitably the disease or

30

1	disorder is ischaemia-reperfusion injury or
2	Alzheimer's disease.
3	
4	The composition described above may be used
5	prophylactically or curatively.
6	
7	According to a further aspect of the present
8	invention there is provided a method of
9	manufacturing a compound of Formula 1 as described
10	above, said method comprising providing an
11	intermediate compound A and an intermediate
12	compound B, wherein intermediate compound A has the
13	structure $R_{A}M$ wherein M is a metal or metalloid
14	group (such as ZnCl ₂ , B(OH) ₂ ,
15	9-boracyclo[3.3.1]nony1, $SnBu_3$ or $MgBr$) where the
16	metal is directly attached to R_{A} , and R_{A} is a C_{2} to
17	C_{30} saturated or unsaturated alkyl chain which may
18	optionally be substituted with small alkyl groups
19	such as CH_3 and C_2H_5 , and R_AM is capable of
20	participating in transition metal catalysed cross-
21	coupling reactions;
22	
23	and intermediate compound B has the following
24	structure:
25	

$$(X)_{m}$$
 $(X)_{m}$
 $(X)_$

1

- 2 wherein
- 3 R_{12} represents OH or an O-protecting group
- 4 R_3 , R_{10} , R_{11} , R_{13} , and R_{14} each independently
- 5 represent H, OH, C1 to C4 aliphatic alkyl group or
- 6 an O-protecting group where required, and
- 7 optionally there is a double bond between C2 and C3
- 8 of the C ring;
- 9 X is a halogen, O-trifluoromethane sulphonate or
- 10 any other group used in cross-coupling reactions;
- 11 and
- 12 m = 1 or 2 (ie 1 or 2 groups may be attached to the
- 13 A Ring),

14

- 15 and reacting intermediate compound A with
- 16 intermediate compound B by transition metal
- 17 catalysed cross-coupling reactions and subsequently
- 18 deprotecting at least one OH group.

19

- 20 Preferably R_nM is an organomagnesium, organozinc,
- 21 organoboron or organotin compound. Alternatively M
- 22 may be a silyl group.

- 24 The transition metal catalyst may be any suitable
- 25 transition metal catalyst used in cross-coupling

1 reactions and particular mention may be made of

2 palladium, nickel or iron complexes.

3

4 The protecting group may suitably be methoxymethyl,

5 benzyl (with an optionally substituted aromatic

6 ring), tetrahydropyranyl (THP), or a small alkyl

7 group such as methyl.

8

9 Usually all of the OH groups will be protected but

10 it may be possible that certain groups need not be

11 protected under certain reaction conditions. In

12 particular R3 can be OH.

13

14 According to an alternative embodiment, there is

15 provided a method of manufacturing a compound of

16 Formula 1 as described above, said method

17 comprising providing an intermediate compound C and

18 an intermediate, wherein said intermediate compound

19 C has the structure R_ACHCHR wherein R_A is as

20 defined above for Formula 1,

21 and wherein intermediate compound D has the

22 following structure:

23

24 25

26 wherein R₁₂ represents OH or an O-protecting group;

 R_{3} , R_{10} , R_{11} , R_{13} and R_{14} each independently represent

28 H, OH, C1-4 aliphatic alkyl or an O-protecting group

1 where required; and RB is as defined for Formula 1

2 or is an allyl group capable of cross-metathesis,

3

4 and reacting intermediate compound C with

- 5 intermediate compound D by cross-metathesis in the
- 6 presence of an alkene cross-metathesis catalyst and
- 7 subsequently deprotecting at least one OH group.

8

9 Suitable exemplary alkene cross-metathesis

10 catalysts are set out below:

11

PCy₃

$$Ru = Cl$$
 $Ru = Ru$
 Ru
 $Ru = Ru$
 Ru
 Ru

12

13 A reaction scheme for cross-metathesis on the

- 14 flavonoid as described above is presented for
- 15 clarity (all definitions are as given above).

$$R_{10}$$

$$R_{12}$$

$$R_{12}$$

$$R_{13}$$

$$R_{14}$$

$$R_{12}$$

$$R_{13}$$

$$R_{14}$$

$$R_{12}$$

$$R_{13}$$

$$R_{14}$$

$$R_{12}$$

$$R_{14}$$

$$R_{15}$$

16

17

18 Alternative methods of manufacturing a compound

19 according to Formula 1 are also possible.

- 1 Thus, the present invention provides a method
- 2 wherein the side-chain is attached to the A-ring by
- 3 a cross-coupling or cross-metathesis reaction to
- 4 provide a substituted phenyl which is subsequently
- 5 used as a reactant to construct the flavonol core
- 6 according to known methodology, for example Algar-
- 7 Flynn-Oyamada (AFO) oxidation or Baker-Venkataraman
- 8 rearrangement/cyclisation (see Wagner in "The
- 9 Flavanoids", Chapman and Hall; London 1975; pages
- 10 144 to 146).

- 12 A cross-coupling reaction scheme suitable to
- 13 manufacture an intermediate for production of a
- 14 compound of Formula 1 is represented below:

$$X + \bigvee_{R}^{O-R_C}$$

transition metal catalysed cross coupling

 R_AM

$$R_A$$

15

16 or

$$X \xrightarrow{R_B} R$$

transition metal catalysed cross coupling

$$R_AM$$

$$R_A$$

17

18

- 19 wherein
- 20 R represents H, COCH3, COCH2OCH3, COCH2OPG (where
- 21 "PG" is any suitable protecting group as discussed
- 22 above) or COCH=CHAr (where "Ar" is any aromatic
- 23 group);

24

25 R_c is H or a protecing group.

- 1 X is a halogen, O-trifluoromethane sulphonate or
- 2 any other group used in cross-coupling reactions;
- 3 R_B is as defined in Formula 1 or an allyl group
- 4 capable of cross-metathesis; and
- 5 R_AM is as defined above for intermediate compound
- 6 A.

- 8 Alternatively the intermediate group can be
- 9 obtained by cross-metathesis. A cross-metathesis
- 10 reaction scheme suitable to manufacture an
- 11 intermediate for production of a compound of
- 12 Formula 1 is represented below:

 $= \bigvee_{R}^{O-R_C}$

Alkene cross-metathesis

RAnna O-RC

13

14

 \sim O-R_C

$$R_{R}$$

Alkene cross-metathesis catalyst

$$R_{A_{n_{n_{n}}}}$$
 $O-R_{C}$

- 16 wherein
- 17 R represents H, COCH3, COCH2COCH3, COCH2OPG (where
- 18 "PG" is any suitable protecting group as discussed
- 19 above or COCH2=CHAr (where "Ar" is any aromatic
- 20 group);
- 21 R_D represents H, a C_{1-6} alkyl or aryl group or a
- 22 group RA;
- 23 R_A is as defined above for Formula 1;

1 Rc is H or a protecting group; and

2

3 R_B is as defined in Formula 1 or is an allyl group

4 capable of cross-metathesis.

5

6 A typical reaction scheme (Reaction Scheme A) can

7 be represented as:

8

9

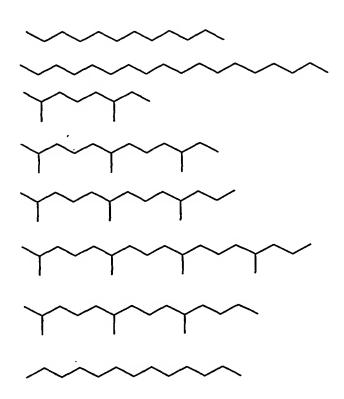
10 Reaction Scheme A

11

12 R_A of Reaction Scheme A is as defined above for

13 Formula 1. Exemplary RA sidechains are:

1



2

3 An alternative generic reaction scheme (Reaction

4 Scheme B) is:

5

6

$$CF_{5}SO_{2}O \longrightarrow OH \longrightarrow CO_{2}H \longrightarrow CO_{2}H \longrightarrow CO_{2}H \longrightarrow CH_{2}CI_{2}$$

$$CF_{5}SO_{2}O \longrightarrow OH \longrightarrow CO_{2}H \longrightarrow CO_{2}H \longrightarrow CH_{2}CI_{2}$$

$$MeO \longrightarrow CO_{2}H \longrightarrow CH_{2}CI_{2}$$

$$MeO \longrightarrow OMe \longrightarrow OMe$$

$$CO_{2}H \longrightarrow CH_{2}CI_{2}$$

$$OMe \longrightarrow OMe$$

2 Reaction Scheme B

3

1

4 RA typically represents any alkyl chain as defined

5 above for Formula 1.

6

7 A further alternative reaction scheme (Reaction

8 Scheme C) is:

Reaction Scheme C

4

3

5 Again, R_A is as defined above in Formula 1.

6 A yet further alternative reaction scheme (Reaction

7 Scheme D) is:

8

9

10

2 Reaction Scheme D

3 4

1

R_A is as defined above in Formula 1.

5

6 A yet further alternative reaction scheme (Reaction

7 Scheme E) is:

8

9

10

11

12

2 Reaction Scheme E

3

1

4 RA is again as previously defined.

5

- 6 Reaction Scheme F shows a suitable purification
- 7 procedure.

OAc

OAc

29

Reaction Scheme F 1 2 3 RA is again as previously designed. 4 R_{B} is as R_{A} but can also be M. 5 6 The present invention will now be further described 7 8 by reference to the non-limiting examples and 9 figures in which: 10 Fig. 1 shows the decay curve of the galvinoxyl 11 resonance obtained in ESR timesweep mode (static 12 field) during in situ reduction of the radical by 13 Inset is the fieldsweep spectrum of 14 quercetin. 15 galvinoxyl. 16 17 Fig. 2 shows the efficacy of target compounds of varying chain length at inhibiting lipid 18 19 peroxidation by measuring their inhibition of TBARS 20 production. 21 22 Fig. 2a shows the efficacy of target compounds of 23 different head group and chain attachment at 24 inhibiting lipid peroxidation by measuring their 25 inhibition of TBARS production. 26 27 Fig. 3a is a scatter plot of the data shown in Fig. 28 2. 29 30 Fig. 3b is a scatter plot of the data shown in Fig. 31 4.

1 Example 1

2

- 3 7-Ethyl-3-hydoxy-2-(3,4,5-trihydoxy-phenyl)-
- 4 chromen-4-one (compound 9c) was prepared by
- 5 synthesis from the corresponding acetophenone by
- 6 aldol condensation to give a chalcone, then Algar-
- 7 Flynn-Oyamada (AFO) Oxidation to give a flavonol
- 8 and followed by deprotection as follows:

9

- 10 1-(4-Ethyl-2-hydroxy-phenyl)-ethanone (18)
- 11 To aluminium chloride (23 g, 172 mmol, 1.9 equ) was
- 12 added 3-ethyl-phenyl-acetate (14.82 g, 90 mmol)
- 13 dropwise. The mixture was heated to 130°C for 150
- 14 minutes then cooled. 2M HCl (50 ml) was added
- 15 slowly and the mixture stirred for 45 minutes, then
- 16 poured into 2M HCl (85 ml) and extracted into
- 17 diethyl ether (2x). The combined organic layers
- 18 were washed with water, 1% sodium carbonate, water
- 19 then dried (MgSO₄) and concentrated in vacuo to
- 20 give 18 (10.8 g, 97 %) as a brown oil.

21

- 24 ¹H nmr (400 MHz, CDCl₃) 1.81 (t, 3H, 7.6 Hz) 2.60-
- 25 2.63 (m, 5H) 6.74 (dd, 1H, 1.5+8 Hz) 6.79 (s, 1H)
- 26 7.63 (d, 1H, 8 Hz) 12.28 (s, 1H). ¹³C nmr (100 MHz,
- 27 CDCl₃) 15.12 (CH₃) 26.87 (CH₃) 29.53 (CH₂) 117.55
- 28 (CH) 118.12 (Q) 119.46 (CH) 131.09 (CH) 154.62 (Q)
- 29 163.01 (Q) 204.28 (Q). EI+ 164.1 (30%, M⁺) 149.1

1 (100%, $[M-Me]^+$) $C_{10}H_{12}O_2$ Calc. 164.0837 Found

2 164.0836.

3

4 <u>1-(4-Ethyl-2-hydroxy-phenyl)-3-(3,4,5-trimethoxy-</u>

5 phenyl)-propenone (22)

6 To a stirring suspension of 18 (5.00 g, 30 mmol)

7 and 3,4,5-trimethoxy benzaldehyde (7.20 g, 37 mmol,

8 1.2 eq) in ethanol (145 ml) was added potassium

9 hydroxide (4.21 g, 7.5 mmol, 2.5 eq). The reaction

10 mixture was stirred for 200 hours then acidified (1

11 N HCl) and extracted with DCM (3x). The combined

12 organic layers were then washed with saturated

13 aqueous sodium bicarbonate, 10 % sodium bisulfite

14 solution and then saturated aqueous sodium

15 bicarbonate again. The organic layer was then dried

16 (MgSO₄) and concentrated in vacuo to give 22 (9.62

17 g, 92 %) as a brown tar.

18

OH O OMe OMe

19 20

21 EI+ 342.2 (100%, M⁺) C₂₀H₂₂O₅ Calc. 342.1467 Found

22 342,1467.

23

24 <u>7-Ethyl-3-hydroxy-2-(3,4,5-trimethoxy-phenyl)-</u>

25 <u>chromen-4-one</u> (26)

26 To a stirring solution of 22 (1.60 g, 4.7 mmol) in

27 methanol (45 ml) and 16 % aqueous sodium hydroxide

28 solution (6.5 ml, 26 mmol, 5.6 equ) at 0°C was

32

1 added 15 % aqueous hydrogen peroxide (6.5 ml, 29

2 mmol, 6.1 equ) dropwise. The solution was stirred

3 at 0°C for ten minutes then sealed and placed in a

4 refrigerator for 26 hours. The reaction was then

5 acidified (2N HCl) and extracted with

6 dichloromethane (3x). The organic layer was then

7 dried (MgSO₄) and concentrated to give a brown oil.

8 This was taken up in dichloromethane, washed with

9 10% sodium bisulfite solution, dried (MgSO₄) and

10 concentrated to give 26 (0.777 g, 47 %) as a yellow

11 solid. This was used without further purification.

12

13 14

15 7-Ethyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-

16 chromen-4-one (9c)

17 To a stirring solution of 26 (0.504 g, 1.4 mmol) in

18 dichloromethane (50 ml) under Ar at 0°C was added

19 boron tribromide in dichloromethane (1.0M, 10 ml,

20 10 mmol, 7 equ). The mixture was warmed to room

21 temperature and then stirred for 21 hours. The

22 reaction was then cooled to 0°C and methanol (10

23 ml) added. The reaction was heated to reflux for 3

24 hours, then concentrated in vacuo to give an orange

25 solid. Water (50 ml) was added and stirred for two

26 hours then left to stand overnight then 9c (0.313

27 g, 70 %) was collected as a black solid.

1 2

 1 H nmr (400 MHz, $D_{3}CCOCD_{3}$) 1.32 (t, 3H, 7.5 Hz),

4 2.81-2.89 (m, 2H), 7.33 (d, 1H, 8.0 Hz), 7.48 (s,

5 2H), 7.53 (s, 1H), 8.04 (d, 1H, 8.0 Hz). 13 C nmr

6 (100 MHz, D₃CSOCD₃) 15.23 (CH₃) 28.53 (CH₂) 107.56

7 (CH) 116.64 (CH) 119.58 (Q) 121.58 (Q) 124.97 (CH)

8 125.15 (CH) 135.99 (Q) 138.19 (Q) 146.07 (Q) 146.13

9 (Q) 150.59 (Q) 154.89 (Q) 172.61 (Q). FAB+ 315.1

10 (8%, $[M+H]^+$), 314.1 (5%, M^+) $C_{17}H_{15}O_6$ calc. 315.0869,

11 found 315.0869.

12

13 The reaction may be summarised by the following

14 Scheme.

OMe CH₂CH₂ CH₂CH₂ **OMe** 70% ОН li O) O 26 9c

1 2

3

Example 2 4

5

- 7-Butyl-3-hydroxy-2-(3,4,5-trihydroxyphenyl)-6
- chromen-4-one (9d) was synthesised from 3-7
- iodophenol (see summary in Scheme 2). 8
- acetophenone (29) was prepared by acetylation of 3-9
- iodophenol and Fries rearrangement as described by 10
- Chen et al. (J Chem Soc (1958) pages 146-150). 11
- Details are as follows: 12

- 2-Hydroxy-4-iodo acetophenone (29) 14
- To a stirring solution of 3-iodo phenyl acetate 15
- (32.20 g, 123 mmol) in chlorobenzene (250 ml) under 16

1 nitrogen was added aluminium chloride (31.00 g, 232

- 2 mmol, 1.9 equ). The reaction mixture was heated to
- 3 140°C for 90 hours then allowed to cool. The
- 4 reaction mixture was poured onto ice/water and then
- 5 filtered, and the residue washed with
- 6 dichloromethane. The filtrate was then extracted
- 7 with dichloromethane and the combined organic
- 8 layers extracted with 10 % potassium hydroxide
- 9 solution (3x 100 ml). The combined aqueous layers
- 10 were then acidified with 6N hydrochloric acid and
- 11 extracted with dichloromethane (3x 75 ml). This
- 12 organic layer was then dried (MgSO4) and
- 13 concentrated in vacuo to give 29 (22.3 g, 69 %) as
- 14 a brown solid.

15

16 17

- 18 1 H nmr (400 MHz, CDCl₃). 2.60 (s, 3H) 7.26-7.28 (m,
- 19 2H) 7.42 (s, 1H) 12.26 (s, 1H). 13C nmr (100 MHz,
- 20 CDCl₃) 26.596 (CH₃), 103.768 (Q), 118.997 (Q),
- 21 127.833 (CH), 128.325 (CH), 131.251 (CH), 162.191
- 22 (Q), 204.214 (Q). CI+ 263.0 (98.%, M+H+) 262 (100%,
- 23 M⁺). Acc.Mass. (M+H) $C_8H_8O_2I$, calc. 262.9569, found
- 24 262.9568. ir (GG) 2360g 1699g 1558g 1205. mp. 51.5-
- 25 52°C (lit. 52-54°C*).

- 27 2'-Hydroxy-4'-iodo-3,4,5-trimethoxy-chalcone (32)
- 28 To a stirring suspension of 29 (0.55 g, 2.1 mmol)
- and 3,4,5-trimethoxy-benzaldehyde (0.66 g, 3.4
- 30 mmol, 1.6 equ) in ethanol (10 ml) was added

36

1 potassium hydroxide (0.25 g, 4.5 mmol, 2.1 equ).

- 2 The reaction mixture was stirred for 119 hours then
- 3 diluted with water, acidified (1N HCl) and
- 4 extracted with ethyl acetate (3x 70 ml). The
- 5 combined organic layers were then washed with
- 6 saturated aqueous sodium bicarbonate (50 ml),
- 7 saturated brine (50 ml), 10 % sodium bisulfite
- 8 solution (3x 50 ml) and then saturated brine (50
- 9 ml) again. The organic layer was then dried (MgSO₄)
- 10 and concentrated in vacuo to give a yellow solid
- 11 (1.17 g). This solid was heated in methanol, and
- 12 the undissolved solid collected. The filtrate was
- 13 concentrated and then heated in methanol again.
- 14 More undissolved solid was collected. Undissolved
- 15 solid is 32 (0.50 g, 54 %).

16

- 19 1 H nmr (400 MHz, CDCl₃) 3.92 (s, 3H) 3.94 (s, 6H)
- 20 6.88 (s, 2H) 7.30 (dd, 1.6+8 Hz, 1H) 7.42-7.47 (m,
- 21 2H) 7.59 (d, 8 Hz, 1H) 7.86 (d, 15 Hz, 1H) 12.89
- 22 (s, 1H). ¹³C nmr (100 MHz, CDCl₃) 56.268 (CH₃),
- 23 61.021 (CH₃), 103.699 (CH), 103.699 (Q), 106.054
- 24 (CH), 118.683 (CH), 119.317 (Q), 128.010 (CH),
- 25 128.128 (CH) 129.802 (Q), 130.126 (CH), 146.271
- 26 (CH), 153.519 (Q), 163.378 (Q), 193.146 (Q). EI+
- 27 439.9 (100 %, M⁺). Acc.Mass. C₁₈H₁₇O₅I, calc.

1 440.0121, found 440.0118. ir (GG) 2360, 1716, 1684.

2 mp 140.5-140.9°C.

3

- 4 3-Hydroxy-7-iodo-2-(3,4,5-trimethoxyphenyl)-
- 5 chromen-4-one
- 6 To a stirring solution of 32 (0.165 g, 0.4 mmol) in
- 7 methanol (4.4 ml) and 16 % aqueous sodium hydroxide
- 8 solution (0.6 ml, 2.4 mmol, 6.4 equ) at 0°C was
- 9 added 15 % aqueous hydrogen peroxide (0.6 ml, 2.6
- 10 mmol, 7.1 equ) dropwise. The solution was stirred
- 11 at 0°C for ten minutes then sealed and placed in a
- 12 refrigerator for 24 hours. The reaction was then
- 13 filtered and then collected solid separated between
- 14 1N HCl and dichloromethane. The organic layer was
- 15 then dried (MgSO₄) and concentrated to give 3-
- 16 hydroxy-7-iodo-2-(3,4,5-trimethoxyphenyl)-chromen-
- 17 4-one as a yellow solid. Meanwhile filtrate was
- 18 acidified (1N HCl) and the precipitated solid, 3-
- 19 hydroxy-7-iodo-2-(3,4,5-trimethoxyphenyl)-chromen-
- 20 4-one, collected. (Total yield 0.130 g, 76 %).

- 23 ¹H nmr (400 MHz, CDCl₃) 3.95 (s, 3H) 3.97 (s, 6H)
- 24 7.03 (br s, 1H) 7.51 (s, 2H) 7.72 (dd, 1.4+8 Hz,
- 25 1H) 7.93 (d, 8 Hz, 1H) 8.05 (d, 1.4 Hz, 1H). ¹³C
- 26 nmr (100 MHz, CDCl₃) 56.302 (CH₃), 61.011 (CH₃),
- 27 100.113 (Q), 105.370 (CH), 119.947 (Q), 125.788
- 28 (Q), 126.518 (CH), 127.348 (CH), 133.869 (CH)

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38

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138.331 (Q), 140.160 (Q), 144.704 (Q), 153.227 (Q),
1
    154.780 (Q), 172.825 (Q). EI+ 453.9 (100 %, M<sup>+</sup>)
2
    438.9 (25%, M-CH<sub>3</sub>^{+}). Acc.Mass. C<sub>18</sub>H<sub>15</sub>O<sub>6</sub>I, calc.
3
    453.9913, found 453.9916. ir (GG) 3749, 2360, 1734,
4
    1265, 740. mp 151-153°C.
5
6
    3-Benzyloxy-7-iodo-2-(3,4,5-trimethoxy-phenyl)
7
    chromen-4-one (34)
8
    A stirring suspension of 3-hydroxy-7-iodo-2-(3,4,5-
9
    trimethoxyphenyl)-chromen-4-one (0.257 g, 0.6mmol),
10
    potassium carbonate (1.48 g, 11mmol, 19 equ),
11
    potassium iodide (0.06 g, 0.3 mmol, 0.6 equ) and
12
    benzyl chloride (0.16 ml, 1.3 mmol, 2.3 equ) in
13
    acetone (12 ml) under nitrogen was heated to reflux
14
    for one hour. The reaction was filtered and the
15
     filtrate concentrated in vacuo to give an orange
16
     solid. This solid was recrystallised from
17
     isopropanol to give 34 (0.270 g, 88 %) as a white
18
     solid.
19
20
     The substituted flavonol 9d was further purified by
21
     treatment with acetic anhydride (6 eq.) and N, N-
22
     dimethyl-4-aminopyridine (0.05 eq.) in pyridine (60
23
     eq.). When the reaction was complete, this was
24
     diluted with ethyl acetate and washed with dilute
25
     hydrochloric acid and saturated sodium bicarbonate
26
     solution. The organic solution was then dried
27
     (MgSO<sub>4</sub>) and concentrated to give the crude
28
     tetraacetate derivative. Recrystallization from
29
     methanol gave the pure substituted tetraacetate,
```

0.05M) containing catalytic concentrated

30

31

32

which was deprotected by heating in methanol (ca.

1 hydrochloric acid for 1 hour. Dilution with water

2 gave the substituted flavonol 9d as a fine yellow

3 precipitate that was collected by filtration or

4 extraction into ethyl acetate.

5

6 7

8 1 H nmr (400 MHz, CDCl₃) 3.79 (s, 6H) 3.95 (s, 3H)

9 5.15 (s, 2H) 7.28-7.30 (m, 5H) 7.35-7.37 (m, 2H)

10 7.76 (d, 8 Hz, 1H) 7.99-8.01 (m, 2H). ¹³C nmr (100

11 MHz, CDCl₃) 56.110 (CH₃), 60.9670 (CH₃), 74.493

12 (CH₂), 99.720 (Q), 106.333 (CH), 123.518 (Q),

13 125.565 (Q), 126.992 (CH), 127.095 (CH), 128.278

14 (CH) 128.830 (CH), 134.025 (CH), 136.538 (Q),

15 152.862 (Q), 154.796 (Q), 155.731 (Q), 174.559 (Q).

16 EI+ 543.9 (30 %, M^{+}) 452.9 (47 %, $M-Bn^{+}$). Acc. Mass.

17 $C_{25}H_{21}O_6I$, calc. 544.0383, found 544.0385. mp.

18 142°C. ir (GG) 2360, 1734, 1558, 1265, 744.

19

3-Benzyloxy-7-butyl-2-(3,4,5-trimethoxy-phenyl)-

21 chromen-4-one (39d)

22 To a stirring solution of n-butane boronic acid

23 (0.133 g, 1.3 mmol, 1.4 equ) and dichloropalladium

24 (dppf) (0.050 g, 0.06 mmol, 0.07 eq) in

25 tetrahydrofuran (7 ml) and 3M NaOH solution (1.1

26 ml) was added 34 (0.500 g, 0.9 mmol) added and the

27 reaction heated to reflux for 21 hours. The

28 reaction was then quenched with water and diethyl

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40

1 ether. The organic layer was collected and the

- 2 aqueous layer extracted with diethyl ether (2x).
- 3 The combined organic layers were washed with 1M
- 4 HCl and brine then dried (MgSO₄) and concentrated
- 5 in vacuo to give a yellow oil. A silica plug
- 6 (dichloromethane) yielded 39d (0.099 g, 23 %) as an
- 7 orange oil.

8

9 10

- 11 EI+ 474.2 (15%, M⁺) C₂₉H₃₀O₆ Calc. 474.2042 Found
- 12 474.2041.

13

- 14 7-Butyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-
- 15 chromen-4-one (9d)
- 16 To a stirring solution of 39d (0.389 g, 1 mmol) in
- 17 dichloromethane (15 ml) under Ar was added boron
- 18 tribromide in dichloromethane (1.0M, 5.0 ml, 5
- 19 mmol, 4.9 equ). The mixture was then stirred for 18
- 20 hours. Methanol (5 ml) was then added. The reaction
- 21 was heated to reflux for 2 hours, then concentrated
- 22 in vacuo to give a brown solid. Water (25 ml) was
- 23 added and the mixture sonicated then extracted into
- 24 ethyl acetate (3x). The organic layer was washed
- 25 with brine then dried (MgSO₄) and concentrated in
- 26 vacuo to give 9d (0.302 g, 77%) as a brown solid.

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1 2

 1 H nmr (400 MHz, CD₃SOCD₃) 0.92 (t, 3H, 7.3 Hz) 1.34

41

4 (m, 2H) 1.65 (m, 2H) 2.76 (t, 2H, 7.3 Hz) 7.30 (m,

5 3H) 7.48 (s, 1H) 8.00 (d, 1H, 8.1Hz). ¹³C nmr (100

6 MHz, CDCl₃). FAB+ 343.3 (10%, [M+H]⁺) C₁₉H₁₉O₆ calc.

7 343.1182 found 343.1184.CHN $C_{19}H_{18}O_6$ calc. 66.66% C,

8 5.30% H, found 65.31% C, 4.62% H.

9

10 The reaction can be summarised as follows:

11

12

13

14

AlCl₃, PhCl (69%)

i) H₂O₂, NaOH MeOH

ii) BnCl, K₂CO₃, Kl, acetone

OMe

Cl₂Pd(dppf), NaOH_(aq), THF

i) BBr₃, CH₂Cl₂

39 R = Me d 23% e 24% e* 49% f 59%

40 R = Bn g 59% h 35% j 68% $d R^{1} = nBu$ $e R^{1} = nC_{6}H_{13}$ $e^{*} R^{1} = Me_{2}CH(CH_{2})_{3}$ $f R^{1} = nC_{8}H_{17}$ $g R^{1} = nC_{10}H_{21}$ $h R^{1} = nC_{12}H_{25}$ $i R^{1} = nC_{18}H_{37}$

9 (from 39) d 77% e 93% e* 91% f 71% (from 40) g 95% h 35% j 99%

OH

1

2

1 Example 3

2

- 3 7-Hexyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-
- 4 chromen-4-one (9e) was synthesised in a similar
- 5 manner to that described in Example 2.

6

- 7 3-Benzyloxy-7-hexyl-2-(3,4,5-trimethoxy-phenyl)-
- 8 chromen-4-one (39e)
- 9 To a stirring solution of 1-hexene (0.109 g, 1.3
- 10 mmol, 1.4 eq) in tetrahydrofuran (2 ml) under argon
- 11 at 0°C was added 9-BBN in tetrahydrofuran (0.5M,
- 12 2.7 ml, 1.4 mmol, 1.5 eq). The reaction was allowed
- 13 to warm to room temperature and stirred for 8 hours
- 14 then 34 (0.505 g, 0.9 mmol) (produced as described
- 15 in Example 2) in tetrahydrofuran (5 ml), 3M NaOH
- 16 solution (1.1 ml) and dichloropalladium (dppf)
- 17 (0.032 g, 0.04 mmol, 0.04 eq) were added and the
- 18 reaction heated to reflux for 15 hours. The
- 19 reaction was then quenched with water and diethyl
- 20 ether. The organic layer was collected and the
- 21 aqueous layer extracted with dichloromethane. The
- 22 combined organic layers were dried (MgSO₄) and
- 23 concentrated in vacuo to give a brown oil. Column
- 24 chromatography (silica gel, DCM) yielded 39e (0.112
- 25 g, 24 %) as a colourless oil.

26

27

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44

- 1 ¹H nmr (400 MHz, CDCl₃) 0.89 (t, 3H, 6.5 Hz) 1.30-
- 2 1.42 (m, 6H) 1.66-1.73 (m, 2H) 2.76 (t, 2H, 7.5 Hz)
- 3 3.78 (s, 6H) 3.93 (s, 3H) 5.13 (s, 2H) 7.23-7.37
- 4 (m, 9H) 8.19 (d, 1H, 8.1 Hz). 13 C nmr (100 MHz,
- 5 CDCl₃) 14.45 (CH₃) 22.94 (CH₂) 29.30 (CH₂) 31.35
- 6 (CH₂) 32.03 (CH₂) 32.44 (CH₂) 36.50 (CH₂) 56.52
- 7 (CH₃) 61.35 (CH₃) 74.87 (CH₂) 106.76 (CH) 117.38
- 8 (CH) 122.48 (Q) 125.98 (CH) 126.11 (CH) 126.58 (Q)
- 9 128.55 (CH) 128.64 (CH) 129.25 (CH) 137.23 (Q)
- 10 140.30 (Q) 140.48 (Q) 150.22 (Q) 153.23 (Q) 155.75
- 11 (Q) 155.92 (Q) 175.38 (Q). EI+ 502.6 (35%, M⁺)
- 12 411.5 (43%, $[M-Bn]^+$) $C_{31}H_{34}O_6$ Calc. 502.2355 Found
- 13 502.2354.

14

- 15 7-Hexyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-
- 16 chromen-4-one (9e)
- 17 To a stirring solution of 39e (0.096 g, 0.2 mmol)
- 18 in dichloromethane (10 ml) under Ar at 0°C was
- 19 added boron tribromide in dichloromethane (1.0M,
- 20 1.0 ml, 1.0 mmol, 5.2 equ). The mixture was warmed
- 21 to room temperature and then stirred for 15 hours.
- 22 Methanol (5 ml) was then added. The reaction was
- 23 heated to reflux for 100 minutes, then concentrated
- 24 in vacuo to give a red solid. Water (20 ml) was
- 25 added and the mixture sonicated then left to stand
- 26 overnight then 9e (0.066 g, 93 %) was collected as
- 27 a yellow solid.

- 29 The substituted flavonol 9e was further purified by
- 30 treatment with acetic anhydride (6 eq.) and N, N-
- 31 dimethyl-4-aminopyridine (0.05 eq.) in pyridine (60
- 32 eq.). When the reaction was complete, this was

1 diluted with ethyl acetate and washed with dilute

- 2 hydrochloric acid and saturated sodium bicarbonate
- 3 solution. The organic solution was then dried
- 4 (MgSO₄) and concentrated to give the crude
- 5 tetraacetate derivative. Recrystallization from
- 6 methanol gave the pure substituted tetraacetate,
- 7 which was deprotected by heating in methanol (ca.
- 8 0.05M) containing catalytic concentrated
- 9 hydrochloric acid for 1 hour. Dilution with water
- 10 gave the substituted flavonol 9e as a fine yellow
- 11 precipitate that was collected by filtration or
- 12 extraction into ethyl acetate.

13

14

- 15 ¹H nmr (400 MHz, CD₃SOCD₃) 0.86 (t, 3H, 6.0 Hz)
- 16 1.27-1.33 (m, 6H) 1.61-1.68 (m, 2H) 2.75 (t, 2H,
- 17 7.5 Hz) 7.28-7.33 (m, 3H) 7.48 (s, 1H) 7.99 (d, 1H,
- 18 8.1Hz) 8.79 (s, 1H) 9.21 (m, 3H). ¹³C nmr (100 MHz,
- 19 D₃CSOCD₃) 14.29 (CH₃) 22.35 (CH₂) 28.60 (CH₂) 30.64
- 20 (CH₂) 31.39 (CH₂) 35.42 (CH₂) 107.56 (CH) 117.24
- 21 (CH) 119.57 (Q) 121.56 (Q) 124.91 (CH) 125.56 (CH)
- 22 135.98 (Q) 138.18 (Q) 146.06 (Q) 146.06 (Q) 149.298
- 23 (Q) 154.81 (Q) 172.62 (Q). EI+ 370.1 (100%, M⁺)
- 24 $C_{21}H_{22}O_6$ calc. 370.1416 found 370.1414.

25

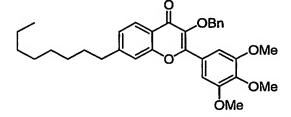
26 Example 4

- 1 7-Octyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-
- 2 chromen-4-one (Compound 9f) was prepared
- 3 analogously to Examples 2 and 3.

4

- 5 3-Benzyloxy-7-octyl-2-(3,4,5-trimethoxy-phenyl)-
- 6 chromen-4-one (39f)
- 7 To a stirring solution of 1-octene (0.148 g, 1.3
- 8 mmol, 1.4 eq) in tetrahydrofuran (2 ml) under argon
- 9 at 0°C was added 9-BBN in tetrahydrofuran (0.5M,
- 10 2.7 ml, 1.4 mmol, 1.5 eq). The reaction was allowed
- 11 to warm to room temperature and stirred for 9 hours
- 12 then 34 (0.504 g, 0.9 mmol) (produced as described
- in Example 2) in tetrahydrofuran (5 ml), 3M NaOH
- 14 solution (1.1 ml) and dichloropalladium (dppf)
- 15 (0.031 g, 0.04 mmol, 0.04 eq) were added and the
- 16 reaction heated to reflux for 15 hours. The
- 17 reaction was then quenched with water and diethyl
- 18 ether. The organic layer was collected and the
- 19 aqueous layer extracted with dichloromethane. The
- 20 combined organic layers were washed with brine
- 21 dried (MgSO₄) and concentrated in vacuo to give a
- 22 orange oil. Column chromatography (silica gel, DCM)
- 23 yielded **39f** (0.290 g, 59 %) as a colourless oil.

24



- 27 ¹H nmr (400 MHz, CDCl₃) 0.88 (t, 3H, 7.0 Hz) 1.25-
- 28 1.41 (m, 10H) 1.62-1.74 (m, 2H) 2.76 (t, 2H, 7.5

- 1 Hz) 3.78 (s, 6H) 3.89 (s, 3H) 5.13 (s, 2H) 7.21-
- 2 7.37 (m, 9H) 8.19 (d, 1H, 8.2 Hz). ¹³C nmr (100
- 3 MHz, CDCl₃) 14.48 (CH₃) 23.03 (CH₂) 29.59 (CH₂)
- 4 29.65 (CH₂) 29.80 (CH₂) 31.40 (CH₂) 32.30 (CH₂)
- 5 36.51 (CH₂) 56.52 (CH₃) 61.35 (CH₃) 74.87 (CH₂)
- 6 106.76 (CH) 117.38 (CH) 122.48 (Q) 125.98 (CH)
- 7 126.11 (CH) 126.58 (Q) 128.55 (CH) 128.64 (CH)
- 8 129.25 (CH) 137.23 (Q) 140.30 (Q) 140.49 (Q) 150.22
- 9 (Q) 153.23 (Q) 155.75 (Q) 155.91 (Q) 175.37 (Q).
- 10 CI+ 531.3 (22%, $[M+H]^+$) $C_{33}H_{39}O_6$ Calc. 531.2747 Found
- 11 531.2744.

12

- 13 7-Octyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-
- 14 chromen-4-one (9f)
- 15 To a stirring solution of 39f (0.290 g, 0.5 mmol)
- 16 in dichloromethane (10 ml) under Ar at 0°C was
- 17 added boron tribromide in dichloromethane (1.0M,
- 18 2.7 ml, 2.7 mmol, 4.9 equ). The mixture was warmed
- 19 to room temperature and then stirred for 16 hours.
- 20 Methanol (5 ml) was then added. The reaction was
- 21 heated to reflux for 2 hours, then concentrated in
- 22 vacuo to give a red solid. Water (25 ml) was added
- 23 and the mixture sonicated then left to stand
- overnight. 9f (0.155 g, 71 %) was collected as a
- 25 yellow solid.

- 27 The substituted flavonol 9f was further purified by
- 28 treatment with acetic anhydride (6 eq.) and N, N-
- 29 dimethyl-4-aminopyridine (0.05 eq.) in pyridine (60
- 30 eq.). When the reaction was complete, this was
- 31 diluted with ethyl acetate and washed with dilute
- 32 hydrochloric acid and saturated sodium bicarbonate

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1 solution. The organic solution was then dried

- 2 (MgSO₄) and concentrated to give the crude
- 3 tetraacetate derivative. Recrystallization from
- 4 methanol gave the pure substituted tetraacetate,
- 5 which was deprotected by heating in methanol (ca.
- 6 0.05M) containing catalytic concentrated
- 7 hydrochloric acid for 1 hour. Dilution with water
- 8 gave the substituted flavonol 9f as a fine yellow
- 9 precipitate that was collected by filtration or
- 10 extraction into ethyl acetate.

11

12 13

- 14 1 H nmr (400 MHz, CD₃SOCD₃) 0.85 (t, 3H, 6.5 Hz)
- 15 1.24-1.30 (m, 10H) 1.63-1.87 (m, 2H) 2.75 (t, 2H,
- 16 7.6 Hz) 7.28-7.34 (m, 3H) 7.48 (s, 1H) 7.99 (d, 1H,
- 17 8.2 Hz) 8.79 (s, 1H) 9.20 (s, 3H). ¹³C nmr (100
- 18 MHz, D₃CSOCD₃) 14.29 (CH₃) 22.41 (CH₂) 28.95 (CH₂)
- 19 29.13 (CH₂) 29.13 (CH₂) 30.66 (CH₂) 31.60 (CH₂)
- 20 35.42 (CH₂) 107.56 (CH) 117.24 (CH) 119.58 (Q)
- 21 121.57 (Q) 124.91 (CH) 125.53 (CH) 135.98 (Q)
- 22 138.19 (Q) 146.06 (Q) 146.06 (Q) 149.27 (Q) 154.80
- 23 (Q) 172.61 (Q). EI+ 398 (16%, M^{+}) $C_{23}H_{26}O_{6}$ calc.
- 24 398.1729 found 398.1733.

25

26 Example 5

- 1 7-(4-Methyl-pentyl)-3-hydroxy-2-(3,4,5-
- 2 trihydroxyphenyl)-chromen-4-one (compound 9e*) has
- 3 a short branched chain and was prepared using a
- 4 similar methodology to Example 2.

- 6 3-Benzyloxy-7-(4-methyl-pentyl)-2-(3,4,5-
- 7 trimethoxy-phenyl)-chromen-4-one (39e*)
- 8 To a stirring solution of 4-methyl pent-1-ene
- 9 (0.110 g, 1.3 mmol, 1.4 eq) in tetrahydrofuran (2
- 10 ml) under argon at 0°C was added 9-BBN in
- 11 tetrahydrofuran (0.5M, 2.7 ml, 1.4 mmol, 1.5 eq).
- 12 The reaction was allowed to warm to room
- 13 temperature then stirred for 6 hours then 34 (0.499
- 14 g, 0.9 mmol) (prepared as described in Example 2)
- in tetrahydrofuran (5 ml), 3M NaOH solution (1.1
- 16 ml) and dichloropalladium (dppf) (0.028 g, 0.03
- 17 mmol, 0.04 eq) were added and the reaction heated
- 18 to reflux for 14 hours. The reaction was then
- 19 quenched with water and diethyl ether. The organic
- 20 layer was collected and the aqueous layer extracted
- 21 with diethyl ether (2x). The combined organic
- 22 layers were washed with 1M HCl and brine then dried
- 23 (MgSO₄) and concentrated in vacuo to give a yellow
- 24 oil. A silica plug (dichloromethane) yielded 39e*
- 25 (0.197 g, 49 %) as a yellow oil.

26

27 28

SUBSTITUTE SHEET (RULE 26)

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50 EI+ 502.3 (6%, M^+) $C_{31}H_{34}O_6$ Calc. 502.2355 Found 1 2 502.2358. 3 7-(4-Methyl-pentyl)-3-hydroxy-2-(3,4,5-trihydroxy-4 phenyl)-chromen-4-one (9e*) 5 To a stirring solution of 39e* (0.184 g, 0.4 mmol) 6 in dichloromethane (20 ml) under Ar at 0°C was 7 added boron tribromide in dichloromethane (1.0M, 8 1.8 ml, 1.8 mmol, 5 equ). The mixture was warmed to 9 room temperature and then stirred for 15 hours. 10 Methanol (10 ml) was then added. The reaction was 11 heated to reflux for 2 hours, then concentrated in 12

13 vacuo to give a brown solid. Water (20 ml) was

14 added and the mixture sonicated then left to stand

overnight. 9e* (0.124 g, 91 %) was then collected

16 as a yellow solid.

17

18 The substituted flavonol 9e* was further purified

19 by treatment with acetic anhydride (6 eq.) and N, N-

20 dimethyl-4-aminopyridine (0.05 eq.) in pyridine (60.

21 eq.). When the reaction was complete, this was

22 diluted with ethyl acetate and washed with dilute

23 hydrochloric acid and saturated sodium bicarbonate

24 solution. The organic solution was then dried

25 (MgSO₄) and concentrated to give the crude

26 tetraacetate derivative. Recrystallization from

27 methanol gave the pure substituted tetraacetate,

which was deprotected by heating in methanol (ca.

29 0.05M) containing catalytic concentrated

30 hydrochloric acid for 1 hour. Dilution with water

31 gave the substituted flavonol 9e* as a fine yellow

precipitate that was collected by filtration or 1

extraction into ethyl acetate. 2

3

4 5

6

¹H nmr (400 MHz, CD₃SOCD₃) 0.86 (d, 6H, 6.6 Hz) 7

1.18-1.24 (m, 2H) 1.51-1.67 (m, 3H) 2.74 (t, 2H, 8

7.5 Hz) 7.30-7.33 (m, 3H) 7.48 (s, 1H) 7.99 (d, 1H,

8.0 Hz) 8.80 (s, 1H) 9.22 (s, 3H). 13 C nmr (100 10

MHz, D_3 CSOCD₃) 22.82 (CH₃) 27.64 (CH) 28.26 (CH₂) 11

35.66 (CH₂) 38.29 (CH₂) 107.56 (CH) 117.24 (CH) 12

119.59 (Q) 121.56 (Q) 124.92 (CH) 125.54 (CH) 13

135.98 (Q) 138.20 (Q) 146.07 (Q) 146.07 (Q) 149.29 14

(Q) 154.81 (Q) 172.61 (Q). EI+ 370.1 (100%, M⁺) 15

 $C_{21}H_{22}O_6$ calc. 370.1416 found 370.1411. 16

17

Example 6 18

19

7-Decyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-20

chromen-4-one (compound 9g) was prepared as 21

22 follows:

23

2-hydoxy-4-iodo acetophenone (29) was prepared as 24

described in Example 2. 25

26

4-Benzyloxy-3,5-dimethoxy-benzaldehyde (31) 27

- 1 To a stirring suspension of syringaldehyde (25.19
- 2 g, 138 mmol) and potassium carbonate (38.14 g, 276
- 3 mmol, 2 equ) in N,N-dimethyl formamide (500 ml) was
- 4 added benzyl bromide (20 ml, 168 mmol, 1.2 equ).
- 5 The reaction was stirred for 25 hours, then poured
- 6 into dichloromethane. The organic solvent was
- 7 washed with water (5x) then dried (MgSO₄) and
- 8 concentrated in vacuo to give a pink oil. This was
- 9 recrystallised from hexane to give 31 (32.9 g, 87
- 10 %).

12

- 13 ¹H nmr (400 MHz, CDCl₃) 3.92 (s, 6H) 5.15 (s, 2H)
- 14 7.13 (s, 2H) 7.28-7.38 (m, 3H) 7.48 (d, 2H, 7.4 Hz)
- 15 9.91 (s, 1H). ¹³C nmr (100 MHz, CDCl₃) 56.638 (CH₃)
- 16 75.428 (CH₂) 105.085 (CH) 128.479 (CH) 128.615 (CH)
- 17 128.803 (CH) 132.286 (Q) 137.591 (Q) 142.790 (Q)
- 18 154.384 (Q) 191.491 (CH). EI+ 272.0 (15 %) M, 91.1
- 19 (100 %) Bn. $C_{16}H_{16}O_4$ calc. 272.1049, obs. 272.1053.
- 20 mp 56-57 °C

- 22 2'-Hydroxy-4'-iodo-4-benzyloxy-3,5-dimethoxy
- 23 chalcone (33)
- 24 To a stirring suspension of 29 (0.73 g, 2.8 mmol)
- 25 and 31 (0.911 g, 3.3 mmol, 1.2 equ) in ethanol (10
- 26 ml) was added potassium hydroxide (0.42 g, 7.5
- 27 mmol, 2.7 equ). The reaction mixture was stirred
- 28 for 46 hours then diluted with water, acidified (2N
- 29 HCl) and extracted with ethyl acetate (3x). The

1 organic layer was then dried (MgSO₄) and

2 concentrated in vacuo to give a brown oil. This

3 solid was recrystallised from methanol to give 33

4 (1.06 g, 74 %) as yellow crystals.

5

6 7

8 1 H nmr (400 MHz, CDCl₃) 3.89 (s, 6H) 5.09 (s, 2H)

9 6.85 (s, 2H) 7.25-7.49 (m, 7H) 7.57 (d, 1H, 8.5 Hz)

10 7.83 (d, 1H, 15 Hz) 12.91 (s, 1H). 13C nmr (100

11 MHz, CDCl₃) 56.668 (CH₃) 75.534 (CH₂) 104.096 (Q)

12 106.543 (CH) 119.064 (CH) 119.757 (Q) 128.424 (CH)

13 128.547 (CH) 128.607 (CH) 128.843 (CH) 130.360 (Q)

14 130.549 (CH) 137.792 (Q) 140.340 (Q) 146.746 (CH)

15 154.256 (Q) 163.807 (Q) 193.575 (Q). EI+ 516.0 (42

16 %, M⁺), 425.0 (74 %, [M-Bn]⁺) 91.0 (100 %, Bn⁺).

17 $C_{24}H_{21}IO_5$ calc. 516.0434, obs. 516.0433. mp 123.6-

18 124.6°C (MeOH).

19

20 3-Hydroxy-7-iodo-(4-benzyloxy-3,5-dimethoxyphenyl)-

21 chromen-4-one

22 To a stirring solution of 33 (0.85 g, 1.6 mmol) in

23 methanol (17 ml) and 16 % aqueous sodium hydroxide

24 solution (2.2 ml, 8.8 mmol, 5.3 equ) at 0°C was

25 added 15 % aqueous hydrogen peroxide (2.2 ml, 9.7

26 mmol, 5.9 equ) dropwise. The solution was stirred

27 at 0°C for ten minutes then sealed and placed in a

28 refrigerator for 24 hours. The reaction was then

1 acidified (1N HCl) and extracted with

- 2 dichloromethane (2x). The organic layer was then
- 3 dried (MgSO₄) and concentrated to give a dark
- 4 yellow foam. This was triturated with ethanol to
- 5 give 3-hydroxy-7-iodo-(4-benzyloxy-3,5-
- 6 dimethoxyphenyl)-chromen-4-one (0.84 g, 96 %) as a
- 7 yellow solid.

8

9 10

- 11 1 H nmr (400 MHz, CDCl₃) 3.93 (s, 6H) 5.12 (s, 2H)
- 12 7.04 (brs, 1H) 7.28-7.38 (m, 3H) 7.49-7.52 (m, 4H)
- 13 7.72 (dd, 1H, 1.4+8.4 Hz) 7.92 (d, 1H, 8.4 Hz) 8.03
- 14 (d, 1H 1.4 Hz). EI+ 530.0 (22 %) M, 425.0 (100 %)
- 15 M-Bn, 91.1 (35 %) Bn. $C_{24}H_{19}IO_6$ calc. 530.0226, obs.
- 16 530.0234. mp 169-171°C (EtOH).

- 18 3-Benzyloxy-7-iodo-2-(4-benzyloxy-3,5-dimethoxy
- 19 phenyl) chromen-4-one (35)
- 20 A stirring suspension of 3-hydroxy-7-iodo-(4-
- 21 benzyloxy-3,5-dimethoxyphenyl)-chromen-4-one (5 g,
- 22 9 mmol), potassium carbonate (6.2 g, 45 mmol, 4.8
- 23 equ), potassium iodide (0.64 g, 4 mmol, 0.4 equ)
- 24 and benzyl chloride (1.7 ml, 15 mmol, 1.6 equ) in
- 25 acetone (150 ml) under nitrogen was heated to
- 26 reflux for 19 hours. The reaction was filtered and
- 27 the filtrate concentrated in vacuo to give an cream
- 28 solid. This solid was recrystallised from

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55

isopropanol to give 35 (5.77 g, 99 %) as a white 1

2 solid.

3 4

 1 H nmr (400 MHz, CDCl₃) 3.73 (s, 6H) 5.11 (s, 2H) 5

7.21 (s, 2H) 7.26-7.37 (m, 8H) 7.49 (d, 2H, 7 Hz) 6

7.73 (d, 1H, 8 Hz) 7.97 (m, 2H). ¹³C nmr (100 MHz, 7

CDCl₃) 56.514 (CH₃) 74.869 (CH₂) 75.438 (CH₂) 8

100.103 (Q) 106.777 (CH) 123.930 (Q) 126.104 (Q) 9

127.400 (CH) 127.507 (CH) 128.597 (CH) 128.675 (CH) 10

128.693 (CH) 128.875 (CH) 129.272 (CH) 134.421 (CH) 11

136.926 (Q) 137.831 (Q) 139.591 (Q) 140.456 (Q) 12

153.595 (Q) 155.209 (Q) 156.219 (Q) 174.973 (Q). 13

14 EI+ 620.0 (20 %) M, 528.9 (20 %), 91.1 (100 %) Bn.

15 $C_{31}H_{25}IO_6$ calc. 620.0696, obs. 620.0695. mp 131-

133°C. 16

17

3-Benzyloxy-2-(4-benzyloxy-3,5-dimethoxy-phenyl)-7-18

decyl-chromen-4-one (40g) 19

To a stirring solution of 1-decene (0.176 g, 1.3 20

21 mmol, 1.4 eq) in tetrahydrofuran (2 ml) under argon

22 was added 9-BBN in tetrahydrofuran (0.5M, 2.7 ml,

23 1.4 mmol, 1.5 eq). The reaction was stirred for 6

24 hours then 35 (0.560 g, 0.9 mmol) in

tetrahydrofuran (5 ml), 3M NaOH solution (1.1 ml) 25

and dichloropalladium (dppf) (0.027 g, 0.03 mmol, 26

0.04 eq) were added and the reaction heated to 27

reflux for 15 hours. The reaction was then quenched 28

1 with water and diethyl ether. The organic layer was

2 collected and the aqueous layer extracted with

3 dichloromethane. The combined organic layers were

4 dried (MgSO₄) and concentrated in vacuo to give a

5 brown oil. Column chromatography (silica gel, DCM)

6 yielded 40g (0.339 g, 59 %) as a pale yellow oil.

7

8 9

10 ¹H nmr (400 MHz, CDCl₃) 0.88 (t, 3H, 7 Hz) 1.26-

11 1.42 (m, 14H) 1.65-1.74 (m, 2H) 2.75 (t, 2H, 7 Hz)

12 3.74 (s, 6H) 5.10 (s, 2H) 5.11 (s, 2H) 7.20-7.38

13 (m, 12H) 7.49-7.51 (m, 2H) 8.18 (d, 1H, 8 Hz). 13 C

14 nmr (100 MHz, CDCl₃) 14.11 (CH₃) 22.68 (CH₂) 29.27

15 (CH₂) 29.31 (CH₂) 29.46 (CH₂) 29.55 (CH₂) 29.60

16 (CH₂) 31.01 (CH₂) 31.89 (CH₂) 36.13 (CH₂) 56.14

17 (CH₃) 74.46 (CH₂) 75.06 (CH₂) 106.41 (CH) 117.00

18 (CH) 122.09 (Q) 125.60 (CH) 125.72 (CH) 126.31 (Q)

19 128.00 (Q) 128.17 (CH) 128.21 (CH) 128.26 (CH)

20 128.51 (CH) 128.90 (CH) 136.82 (Q) 137.52 (O)

21 138.24 (Q) 139.99 (Q) 149.82 (Q) 153.16 (Q) 155.37

22 (Q) 155.60 (Q) 175.01 (Q). FAB+ 635.2 (25%, [M+H]*)

23 91.5 (100%, Bn^+) $C_{41}H_{47}O_6$ Calc. 635.3373 Found

24 635.3370.

25

26 7-Decyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-

27 chromen-4-one (9g)

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57

1 To a stirring solution of 40g (0.335 g, 0.5 mmol)

2 in dichloromethane (25 ml) under Ar at 0°C was

3 added boron tribromide in dichloromethane (1.0M, 5

4 ml, 5 mmol, 9.5 equ). The mixture was warmed to

5 room temperature and then stirred for 20 hours. The

6 reaction was then cooled to 0°C and methanol (15

7 ml) added. The reaction was heated to reflux for 3

8 hours, then concentrated in vacuo to give an orange

9 solid. Water (75 ml) was added and sonicated then

10 left to stand overnight then 9g (0.213 g, 95 %) was

11 collected as a yellow solid.

12

13 14

15 ¹H nmr (400 MHz, CD₃COCD₃) 0.88 (m, 3H) 1.26-1.47

16 (m, 14H) 1.75 (m, 2H) 2.78 (m, 2H) 7.34 (d, 1H, 8.0

17 Hz) 7.49 (s, 2H) 7.54 (s, 1H) 7.87 (brs, 1H) 7.93

18 (brs, 1H) 8.05 (d, 1H, 8.0 Hz) 8.19 (s, 2H). 13C

19 nmr (100 MHz, D₃CSOCD₃) 14.28 (CH₃) 22.43 (CH₂)

20 28.90 (CH₂) 29.02 (CH₂) 29.14 (CH₂) 29.28 (CH₂)

21 29.30 (CH₂) 30.64 (CH₂) 31.62 (CH₂) 35.42 (CH₂)

22 107.56 (CH) 117.23 (CH) 119.59 (Q) 121.58 (Q)

23 124.90 (CH) 125.52 (CH) 135.98 (Q) 138.20 (Q)

24 146.06 (Q) 146.11 (Q) 149.25 (Q) 154.81 (Q) 172.60

25 (Q). FAB+ 427.2 (100%, $[M+H]^+$) $C_{25}H_{31}O_6$ calc.

26 427.2121 found 427.2122. CHN $C_{25}H_{30}O_{6}$ calc. 70.18%

27 C, 7.31% H, found 71.96% C, 7.42% H.

1 Example 7

2

- 3 -Hydroxy-2-(3,4,5-trihydroxy-phenyl)-7-dodecyl-
- 4 chromen-4-one (compound 9h) was prepared
- 5 analogously to Example 6.

6

- 7 3-Benzyloxy-7-dodecyl-2-(4-benzyloxy-3,5-dimethoxy-
- 8 phenyl)-chromen-4-one (40h)
- 9 To a stirring solution of 1-dodecene (0.214 g, 1.27
- 10 mmol, 1.4 eq) in tetrahydrofuran (2 ml) under argon
- 11 was added 9-BBN in tetrahydrofuran (0.5M, 2.7 ml,
- 12 1.35 mmol, 1.5 eq). The reaction was stirred for 6
- hours then 31 (prepared as in Example 6) (0.565 g,
- 14 0.9 mmol) in tetrahydrofuran (5 ml), 3M NaOH
- 15 solution (1.1 ml) and dichloropalladium (dppf)
- 16 (0.024 g, 0.03 mmol, 0.03 eq) were added and the
- 17 reaction heated to reflux for 15 hours. The
- 18 reaction was then quenched with 3 N HCl (8 ml),
- 19 diluted with water and extracted into ethyl acetate
- 20 (3x). The combined aqueous layers were dried
- 21 (MgSO₄) and concentrated in vacuo to give a yellow
- 22 oil. Column chromatography (silica gel,
- 23 DCM>DCM:MeOH 99:1) yielded 40h (0.210 g, 35 %) as a
- 24 pale yellow oil.

25

26

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59

- 1 ¹H nmr (400 MHz, CDCl₃) 0.85-0.89 (m, 3H) 1.20-1.37
- 2 (m, 16H) 1.51-1.56 (m, 2H) 1.62-1.71 (m, 2H) 2.75
- 3 (t, 2H, 7.4 Hz) 3.74 (s, 6H) 5.11 (s, 2H) 5.11 (s,
- 4 2H) 7.23-7.38 (m, 13H) 7.50 (dd, 1H, 1.5+6.7 Hz)
- 5 8.19 (d, 1H, 8.2 Hz). ¹³C nmr (100 MHz, CDCl₃) 14.12
- 6 (CH₃) 22.69 (CH₂) 25.75 (CH₂) 27.43 (CH₂) 29.28
- 7 (CH₂) 29.35 (CH₂) 29.47 (CH₂) 29.56 (CH₂) 29.64
- 8 (CH₂) 31.02 (CH₂) 31.92 (CH₂) 36.14 (CH₂) 56.15
- 9 (CH₃) 74.46 (CH₂) 75.06 (CH₂) 106.42 (CH) 118.00
- 10 (CH) 122.10 (Q) 125.60 (CH) 125.73 (CH) 126.32 (Q)
- 11 128.01 (CH) 128.16 (CH) 128.21 (CH) 128.27 (CH)
- 12 128.51 (CH) 128.90 (CH) 136.83 (Q) 137.53 (Q)
- 13 138.94 (Q) 139.88 (Q) 149.82 (Q) 153.17 (Q) 155.37
- 14 (Q) 155.61 (Q) 175.00 (Q). EI+ 662.3 (9%, M⁺) 571.2
- 15 $(12\%, [M-Bn]^+)$ 91.1 $(100\%, Bn^+)$ $C_{43}H_{50}O_6$ Calc.
- 16 662.3607 Found 662.3600. $C_{42}^{13}CH_{50}O_6$ Calc. 663.3641
- 17 Found 663.3636.

- 19 3-Hydroxy-2-(3,4,5-trihydroxy-phenyl)-7-dodecyl-
- 20 chromen-4-one (9h)
- 21 To a stirring solution of 40h (0.058 g, 0.09 mmol)
- 22 in dichloromethane (2.5 ml) under nitrogen at 0°C
- 23 was added boron tribromide (1.0M in DCM, 2.25 ml,
- 24 24 eq). The reaction was then warmed to room
- 25 temperature and stirred for 19 hours. The mixture
- 26 was then cooled to 0°C, methanol (2 ml) added
- 27 heated to reflux for 2 hours. The reaction was then
- 28 cooled and concentrated in vacuo to give a solid
- 29 that was chromatographed (silica gel,
- 30 dichloromethane:methanol, 9:1) to give 9h (0.030g,
- 31 69 %) as a waxy solid.

1 2

3 ¹H nmr 400 MHz, CD₃SOCD₃) 0.84 (t, 3H, 6.4 Hz) 1.18-

4 1.34 (m, 18H) 1.62-1.71 (m, 2H) 2.75 (t, 2H, 7.4

5 Hz) 7.27-7.30 (m, 3H) 7.47 (s, 1H) 7.99 (d, 1H, 8.1

6 Hz). 13C nmr (100 MHz, D₃CSOCD₃) 14.28 (CH₃) 22.42

7 (CH₂) 28.87 (CH₂) 29.02 (CH₂) 29.11 (CH₂) 29.24

8 (CH₂) 29.33 (CH₂) 30.63 (CH₂) 31.61 (CH₂) 35.41

9 (CH₂) 107.56 (CH) 117.24 (CH) 119.58 (Q) 121.57 (Q)

10 124.90 (CH) 125.53 (CH) 135.99 (Q) 138.20 (Q)

11 146.06 (Q) 149.27 (Q) 154.81 (Q) 172.62 (Q). EI+

12 454.2 (29%, M^{+}) $C_{27}H_{34}O_{6}$ calc. 454.2355 found

13 454.2353. FAB+ 455.2 (51%, [M+H]⁺) C₂₇H₃₅O₆ calc.

14 455.2434 found 455.2438.

15

16 Example 8

17

18 3-Hydroxy-7-octadecyl-2-(3,4,5-trihydroxy-phenyl)-

19 chromen-4-one (compound 9j) was prepared

20 analogously to Example 6.

21

22 3-Benzyloxy-2-(4-benzyloxy-3,5-dimethoxy-phenyl)-7-

23 octadecyl-chromen-4-one (40j)

24 To a stirring solution of 1-octadecene (0.322 g,

25 1.3 mmol, 1.4 eq) in tetrahydrofuran (2 ml) under

26 argon was added 9-BBN in tetrahydrofuran (0.5M, 2.7

27 ml, 1.4 mmol, 1.5 eq). The reaction was stirred for

1 6 hours then 35 (prepared as described in Example

2 6) (0.558 g, 0.9 mmol) in tetrahydrofuran (5 ml),

3 3M NaOH solution (1.1 ml) and dichloropalladium

4 (dppf) (0.025 g, 0.03 mmol, 0.04 eq) were added and

5 the reaction heated to reflux for 18 hours. The

6 reaction was then quenched with water and diethyl

7 ether. The organic layer was collected and the

8 aqueous layer extracted with dichloromethane. The

9 combined organic layers were washed with brine,

10 dried (MgSO₄) and concentrated in vacuo to give a

11 brown oil that crystallised on standing. Column

12 chromatography (silica gel, DCM) yielded 40j (0.455

13 g, 68 %) as a white solid.

14

15 16

17 ¹H nmr (400 MHz, CDCl₃) 0.88 (t, 3H, 7 Hz) 1.25-

18 1.39 (m, 30H) 1.69-1.70 (m, 2H) 2.75 (t, 2H, 7.3

19 Hz) 3.74 (s, 6H) 5.10 (s, 2H) 5.11 (s, 2H) 7.21-

20 7.38 (m, 12H) 7.50 (d, 2H, 6.7 Hz) 8.18 (d, 1H, 8

21 Hz). ¹³C nmr (100 MHz, CDCl₃) 14.12 (CH₃) 22.70

22 (CH₂) 29.30 (CH₂) 29.37 (CH₂) 29.48 (CH₂) 29.57

23 (CH₂) 29.67 (CH₂) 29.70 (CH₂) 31.03 (CH₂) 31.93

24 (CH₂) 36.14 (CH₂) 56.14 (CH₃) 74.46 (CH₂) 75.06

25 (CH₂) 106.40 (CH) 117.00 (CH) 122.20 (Q) 125.60

26 (CH) 125.81 (CH) 126.33 (Q) 128.01 (CH) 128.17 (CH)

27 128.21 (CH) 128.26 (CH) 128.51 (CH) 128.90 (CH)

28 140.00 (Q) 149.96 (Q) 153.16 (Q) 155.74 (Q) 174.93

1 (Q). FAB+ 747.3 (22%, [M+H]⁺) 91.5 (100%, Bn⁺)

2 $C_{49}H_{63}O_6$ Calc. 747.4625 Found 747.4622.

3

- 4 3-Hydroxy-7-octadecyl-2-(3,4,5-trihydroxy-phenyl)-
- 5 chromen-4-one (9j)
- 6 To a stirring solution of 40j (0.455 g, 0.6 mmol)
- 7 in dichloromethane (25 ml) under Ar at 0°C was
- 8 added boron tribromide in dichloromethane (1.0M, 6
- 9 ml, 6 mmol, 9.8 equ). The mixture was warmed to
- 10 room temperature and then stirred for 22 hours. The
- 11 reaction was then cooled to 0°C and methanol (25
- 12 ml) added. The reaction was heated to reflux for 2
- 13 hours, then concentrated in vacuo to give a yellow
- 14 solid. Water (50 ml) was added and sonicated then
- 15 left to stand overnight then 9j (0.325 g, 99 %) was
- 16 collected as a yellow solid.

17

ОН

- 20 ¹H nmr (400 MHz, CD₃SOCD₃) 0.84 (t, 3H, 6.2 Hz)
- 21 1.18-1.33 (m, 30H) 1.62-1.70 (m, 2H) 2.73 (d, 2H,
- 22 6.9 Hz) 7.23-7.30 (m, 3H) 7.46 (s, 1H) 7.99 (d, 1H,
- 23 8.1 Hz) 9.18 (s, 3H). ¹³C nmr (100 MHz, D₃CSOCD₃)
- 24 14.28 (CH₃) 22.43 (CH₂) 28.92 (CH₂) 29.04 (CH₂)
- 25 29.14 (CH₂) 29.26 (CH₂) 29.33 (CH₂) 30.67 (CH₂)
- 26 31.63 (CH₂) 35.43 (CH₂) 107.56 (CH) 117.22 (CH)
- 27 119.59 (Q) 121.58 (Q) 124.90 (CH) 125.48 (CH)
- 28 135.97 (Q) 138.20 (Q) 146.06 (Q) 146.10 (Q) 149.22

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63

```
(Q) 154.81 (Q) 172.59 (Q). FAB+ 539.0 (100%,
1
     [M+H]^+) C_{33}H_{47}O_6 calc. 539.3373 found 539.3367. CHN
 2
    C_{33}H_{46}O_6 calc. 73.57% C, 8.61% H, found 73.05% C,
 3
 4
     9.04% H.
 5
 6
    Example 9
 7
     The branched chain flavonoid 7-(3,7-dimethyl-octyl-
 8
     3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one
 9
     (compound 9g*) was synthesised as follows:
10
11
     3,7-Dimethyl-octan-1-ol (43)
12
     A flask containing a stirring suspension of
13
     geraniol (10 ml, 58 mmol) and palladium on carbon
14
     (10% Pd, 0.494 g, 0.08 eq) in ethanol (70 ml) was
15
     evacuated, and then filled with hydrogen. The
16
     reaction mixture was then stirred under an
17
     atmosphere of hydrogen for 21 hours. After this
18
     time the reaction was filtered and the filtrate
19
     concentrated in vacuo to give 43 (5 g, 55 %) as a
20
     colourless oil.
21
22
23
24
     <sup>1</sup>H nmr (400 MHz, CDCl<sub>3</sub>) 0.86-0.90 (m, 10H) 1.11-
25
     1.42 (m, 6H) 1.49-1.68 (m, 3H) 3.63-3.73 (m, 2H).
     <sup>13</sup>C nmr (100 MHz, CDCl<sub>3</sub>) 20.010 (CH<sub>3</sub>), 22.958 (CH<sub>3</sub>),
27
```

26

23.062 (CH₃), 25.051 (CH₂), 28.337 (CH), 29.885 28

(CH), 37.746 (CH₂), 39.629 (CH₂), 40.364 (CH₂), 29

30 61.603 (CH₂).

- 1 1-Iodo-3,7-dimethyl-octane (45)
- 2 To a stirring solution of 43 (5 g, 32 mmol),
- 3 imidazole (2.59 g, 38 mmol, 1.2 eq) and
- 4 triphenylphosphine (9.11 g, 35 mmol, 1.1 eq) in
- 5 toluene (100 ml) under nitrogen was added iodine
- 6 (10.44 g, 41 mmol, 1.3 eq). The reaction mixture
- 7 was stirred for 18 hours then filtered. The
- 8 filtrate was washed with 5 % sodium thiosulfate
- 9 solution (3x 100 ml) then dried (Na₂SO₄) and
- 10 concentrated in vacuo to give a white solid. This
- 11 solid was taken up in hexane (20 ml), cooled and
- 12 filtered. The filtrate was then concentrated in
- 13 vacuo to give 45 (6 g, 71 %) as a colourless oil.

14

16

- 17 ¹H nmr (400 MHz, CDCl₃) 0.86-0.90 (m, 9H) 1.10-1.32
- 18 (m, 6H) 1.49-1.69 (m, 3H) 1.84-1.90 (m, 1H) 3.14-
- 19 3.28 (m, 2H). 13C nmr (100 MHz, CDCl₃) 5.765 (CH₃),
- 20 19.121 (CH₃), 22.970 (CH₂), 24.908 (CH₂), 28.326
- 21 (CH), 34.267 (CH₂), 36.858 (CH₃), 39.562 (CH₂),
- 22 41.371 (CH₂).

- 3-Benzyloxy-2-(4-benzyloxy-3,5-dimethoxy-phenyl)-7-
- 25 (3,7-dimethyl-octyl)-chromen-4-one (47)
- 26 To a stirring suspension of zinc chloride (0.302 g,
- 27 2.2 mmol, 3 eq) and magnesium (0.086, 3.5 mmol, 4.7
- 28 eq) in tetrahydrofuran (2 ml) under argon was added
- 29 45 (0.879 g, 3.3 mmol, 4.4 eq) in tetrahydrofuran
- 30 (2 ml). The reaction was heated to 50°C for 20
- 31 hours then cooled. 35 (prepared as described in

- 1 Example 6) (0.465 g, 0.8 mmol) in tetrahydrofuran
- 2 (6 ml) and dichlorobis-[tri-(o-tolyl)-
- 3 phosphinyl]palladium (0.033 g, 0.04 mmol, 0.06 eq)
- 4 were added and the reaction stirred for 25 hours.
- 5 The reaction was then quenched with 3 N HCl (10
- 6 ml), diluted with water and extracted into
- 7 dichloromethane, washed with brine (2x), dried
- 8 (MgSO₄) and concentrated in vacuo to give a brown
- 9 oil. Column chromatography (silica gel, DCM: MeOH
- 10 1:0>19:1) yielded 47 (0.143 g, 30 %) as a yellow
- 11 oil.

13 14

- 15 FAB+ 635.2 (27%, [M+H]⁺) 545.2 (75%, [M-Bn]⁺) 91.5
- 16 (100%, Bn^+) $C_{41}H_{47}O_6$ Calc. 635.3373 found 635.3374.

- 18 7-(3,7-Dimethyl-octyl)-3-hydroxy-2-(3,4,5-
- 19 trihydroxy-phenyl)-chromen-4-one (9g*)
- 20 To a stirring solution of 47 (0.028 g, 0.05 mmol)
- 21 in dichloromethane (1 ml) under argon at 0°C was
- 22 added boron tribromide (1.0M in DCM, 0.7 ml, 14
- 23 eq). The reaction was then warmed to room
- 24 temperature and stirred for 23 hours. The mixture
- 25 was then cooled to 0°C, methanol (1 ml) added
- 26 heated to reflux for 2 hours. The reaction was then
- 27 cooled and concentrated in vacuo to give a solid

1 that was chromatographed (silica gel, DCM:methanol,

2 19:1) to give 9g* (0.008g, 37 %) as a yellow solid.

3

4 5

6 ¹H nmr (400 MHz, CD₃COCD₃) 0.72-0.74 (m, 6H) 0.85-

7 0.87 (m, 3H) 1.00-1.11 (m, 4H) 1.15-1.30 (m, 4H)

8 1.36-1.47 (m, 2H) 2.61-2.82 (m, 2H) 7.19 (dd, 1H,

9 1.1+7.0 Hz) 7.35 (s, 2H) 7.39 (s, 1H) 7.90 (d, 1H,

10 8.0 Hz). ¹³C nmr (100 MHz, D₃CCOCD₃) 20.26 (CH₃)

11 23.28 (CH₃) 23.36 (CH₃) 25.78 (CH₂) 29.03 (CH) 33.58

12 (CH) 34.54 (CH₂) 38.17 (CH₂) 39.52 (CH₂) 40.40 (CH₂)

13 108.63 (CH) 118.41 (CH) 120.19 (Q) 123.60 (Q)

14 125.98 (CH) 126.55 (CH) 136.38 (Q) 138.99 (Q)

15 146.13 (Q) 146.66 (Q) 151.20 (Q) 156.60 (Q) 173.66

16 (Q). EI+ 426 (100%, M^{+}) $C_{25}H_{30}O_{6}$ calc. 426.2042 found

17 426.2043. CHN $C_{25}H_{30}O_6$ calc. 70.18% C, 7.31% H,

18 found 71.37% C, 7.69% H.

19

20 Example 10

21

22 The branched chain flavonoid 3-hydroxy-2(3,4,5-

23 trihydroxyphenyl) -7-(3,7,11-trimethyl-dodecyl) -

24 chromen-4-one (compound 9i*) was prepared using

25 similar methodology to Example 9.

26

27 Hexahydrofarnesol (44)

1 A flask containing a stirring suspension of

- 2 farnesol (5.7 ml, 22.5 mmol) and palladium on
- 3 carbon (10 % Pd, 1 g, 0.04 equ) in ethanol (15 ml)
- 4 was evacuated, and then filled with hydrogen. The
- 5 reaction mixture was then stirred under an
- 6 atmosphere of hydrogen for 36 hours. After this
- 7 time the reaction was filtered and the filtrate
- 8 concentrated in vacuo to give hexahydrofarnesol
- 9 (44) (4.81 g, 93 %) as a colourless oil.

10

11 12

- 13 ¹H nmr (400 MHz, CDCl₃) Mixture of
- 14 diastereoisomers. 0.84-0.90 (m, 12H) 1.05-1.38 (m,
- 15 13H) 1.49-1.62 (m, 4H) 3.63-3.73 (m, 2H). ¹³C nmr
- 16 (100 MHz, CDCl₃) 11.781 (CH₃), 11.799 (CH₃), 19.585
- 17 (CH₃), 19.643 (CH₃), 20.066 (CH₃), 20.125 (CH₃),
- 18 23.001 (CH₃), 23.092 (CH₃), 24.753 (CH₂), 24.880
- 19 (CH₂) 25.181 (CH₂), 58.359 (CH₃), 29.854 (CH₂),
- 20 29.950 (CH₂), 33.159 (CH), 33.183 (CH), 34.804 (CH)
- 21 37.329 (CH_2), 37.370 (CH_2), 37.679 (CH_2), 37.755
- 22 (CH_2) 37.794 (CH_2), 37.841 (CH_2) 39.752 (CH_2),
- 23 40.363 (CH₂), 61.654 (CH₂). CI+ 246.28 (50 %,
- 24 $M+NH_4^+$) EI+ 210 (12 %, $M-H_2O^+$). Acc.Mass. $C_{15}H_{32}O$,
- 25 $(M-H_2O)$, calc. 210.2348, found 210.2346. ir (thin
- 26 film) 2925, 2360, 2340, 1715, 1459.

- 28 3,7,11-Trimethyl-1-dodecyl iodide (46)
- 29 To a stirring solution of 44 (1.5 g, 6.6 mmol),
- 30 imidazole (1.13 g, 16.6 mmol, 2.5 equ) and
- 31 triphenylphosphine (4.40 g, 16.8 mmol, 2.5 equ) in

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68

- 1 toluene (250 ml) under nitrogen was added iodine
- 2 (3.26 g, 12.8 mmol, 1.9 equ). The reaction mixture
- 3 was stirred for one hour then filtered. The
- 4 filtrate was washed with 8 % sodium thiosulphate
- 5 solution (250 ml) and brine (100 ml) then dried
- 6 (Na₂SO₄) and concentrated in vacuo to give a white
- 7 solid. This solid was taken up in hexane, cooled
- 8 and filtered. The filtrate was then concentrated in
- 9 vacuo to give 46 (1.1 g, 61 %) as a colourless oil.

10

11 12

- 13 ¹H nmr (400 MHz, CDCl₃) 0.84-0.87 (t, 7 Hz, 12H),
- 14 0.95-1.38 (m, 11H), 1.53 (sept, 6.6 Hz, 4H), 1.61-
- 15 1.67 (m, 1H) 1.86-1.89 (m, 1H) 3.13-3.28 (m, 2H).
- 16 13C nmr (100 MHz, CDCl₃) 5.733 (CH₃), 11.799 (CH₂),
- 17 11.818 (CH₂), 19.170 (CH₂), 19.602 (CH₂), 20.087
- 18 (CH₂), 20.087 (CH₂), 23.015 (CH), 23.111 (CH₂),
- 19 24.602 (CH) 25.204 (CH), 28.375 (CH₂). EI+ 338.1 (2
- 20 %, M^+) 211.2 (25 %, $M-I^+$). Acc.Mass. $C_{15}H_{31}I$, calc.
- 21 338.1471, found 338.1472. ir 2955 2360 2340.

- 23 3-Benzyloxy-2-(3,4,5-trimethoxy-phenyl)-7-(3,7,11-
- trimethyl-dodecyl)-chromen-4-one (48)
- 25 To a stirring suspension of zinc chloride (0.367g,
- 26 2.7 mmol, 3 eq) and magnesium (0.100g, 4.1 mmol,
- 27 4.7 eg) in tetrahydrofuran (2.5 ml) under argon was
- 28 added 7 (1.268 g, 3.8 mmol, 4.2 eq) in
- 29 tetrahydrofuran (2.5 ml). The reaction was heated
- 30 to 50°C for 19 hours then cooled. 34 (0.481 g, 0.8
- 31 mmol) in tetrahydrofuran (7 ml) and dichlorobis-

1 [tri-(o-toly1)-phosphinyl]palladium (0.063 g, 0.08

2 mmol, 0.09 eq) added and the reaction stirred for

3 25 hours. The reaction was then quenched with 3 N

4 HCl (10 ml), diluted with water and extracted into

5 ethyl acetate (3x). The combined aqueous layers

6 were dried (MgSO4) and concentrated in vacuo to

7 give a purple oil. Column chromatography (silica

8 gel, petrol:EtOAc 9:1>2:1) yielded 48 (0.082g, 15

9 %) as a pale yellow oil.

10 11

12 ¹H nmr (400 MHz, CDCl₃) 0.84-0.92 (m, 7H), 0.96 (d,

13 6 Hz, 2H), 1.05-1.42 (m, 8H), 1.48-1.70 (m, 12H)

14 2.68-2.83 (m, 2H) 3.78 (s, 6H) 3.93 (s, 3H) 5.13

15 (s, 2H) 7.21-7.37 (m, 9H) 8.19 (d, 8Hz, 1H). 13C

16 nmr (100 MHz, CDCl₃) 19.559 (CH₃), 19.625 (CH₃),

17 19.684 (CH_3), 19.750 (CH_3), 22.629 (CH_3), 22.721

18 (CH₃), 24.382 (CH₂), 24.799 (CH₂), 27.983 (CH),

19 32.603 (CH) 32.783 (CH), 33.743 (CH₂) 37.218 (CH₂),

20 37.281 (CH₂), 37.372 (CH₂), 38.454 (CH₃), 38.552

21 (CH₂), 39.363 (CH₂), 56.153 (CH₃), 60.990 (CH₃),

22 74.507 (CH₂), 106.391 (CH₃) 116.941 (CH₃), 122.079

23 (Q), 125.654 (CH), 126.202 (Q) 128.182 (CH),

24 128.270 (CH) 128.880 (CH), 136.843 (Q) 139.921 (Q),

25 150.178 (Q), 152.857 (Q), 155.406 (Q), 175.015 (Q).

26 EI+ 628.0 (21 %, M^{+}) 537.1 (27 %, $M-Bn^{+}$). Acc. Mass.

27 $C_{40}H_{52}O_6$, calc. 628.3764, found 628.3768. ir (Thin

28 film) 2928, 2360, 2252, 1828, 1457, 908, 734.

1

2 3-Hydroxy-2-(3,4,5-trihydroxy-phenyl)-7-(3,7,11-

3 trimethyl-dodecyl)-chromen-4-one (9i*)

4 To a stirring solution of 48 (0.048 g, 0.08 mmol)

5 in dichloromethane (2.5 ml) under argon at 0°C was

6 added boron tribromide (1.0M in DCM, 2.5 ml, 26

7 eq). The reaction was then warmed to room

8 temperature and stirred for 19 hours. The mixture

9 was then cooled to 0°C, methanol (2 ml) added

10 heated to reflux for 2 hours. The reaction was then

11 cooled and concentrated in vacuo to give a solid

12 that was chromatographed (silica gel,

13 chloroform: methanol, 9:1) to give 9i* (0.033g, 87

14 %) as a waxy solid.

15

OH OH

16 17

18 1 H nmr (400 MHz, CD₃COCD₃) 7.91 (d, 1H, 8 Hz) 7.36

19 (d, 1H, 8 Hz) 7.18 (d, 1H, 8 Hz) 6.91-6.98 (m, 1H)

20 2.52-2.75 (m, 2H) 1.61-0.67 (m, 29H). 13 C nmr (100

21 MHz, CD₃COCD₃) 14.940 (CH₃) 20.292 (CH₃) 20.358

22 (CH₃) 23.325 (CH₃) 23.413 (CH) 25.431 (CH₂) 25.890

23 (CH₂) 29.046 (CH) 29.731 (CH₂) 29.923 (CH₂) 30.116

24 (CH₂) 30.309 (CH₂) 30.502 (CH) 30.694 (CH) 30.887

25 (CH) 31.060 (CH₂) 33.557 (CH) 33.863 (CH) 34.582

26 (CH₂) 38.395 (CH₂) 38.453 (CH₂) 38.472 (CH₂) 40.472

27 (CH₂) 60.979 (CH₂) 108.737 (CH) 118.395 (CH)

28 120.129 (Q) 123.543 (Q) 126.017 (CH) 126.636 (CH)

1 128.927 (CH) 129.468 (CH) 146.672 (CH) 151.261 (CH)

- 2 156.579 (CH) 172.040 (Q). EI+ 496.2 (100 %, M⁺)
- 3 313.1 (60 %, $[M-C_{13}H_{27}]^+$). $C_{30}H_{40}O_6$ calc. 496.2825,
- 4 obs. 496.2823.

5

- 6 The following scheme summarises the production of
- 7 branched chain compounds in Examples 9 and 10.

$$n=1 \text{ or } 2$$

H₂, Pd/ C EtOH

i) Mg, ZnCl₂, THF ii) 0.24 eq. 34 or 35 0.5 mol% [(o-Tol)₃ P]₂PdCl₂ iii) KF

48g* R = Bn, 15% from 35 49i* R = Me, 15% from 34

$$9g^* n = 1,37\%$$
 $9i^* n = 2,87\%$

OH

OH

OH

OH

8

10 Example 11

11

- 12 6-decyl-flavonoid (compound 11g) was prepared by
- 13 the following synthetic route:

- N-(4-Methoxy-phenyl)-acetamide (51)
- 16 To a stirring suspension of p-anisidine (6.036 g,
- 17 49 mmol) in dichloromethane (20 ml) was added

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72

acetic anhydride (5 ml, 53 mmol, 1.1 equ) over one 1

- hour. The reaction was stirred for a further hour 2
- then poured onto hexane (60 ml) and stirred for 3
- another hour. The solid was collected and washed 4
- with hexane to give N-(4-methoxy-phenyl)-acetamide 5
- 51 (7.717 g, 95%) as a pale grey solid. 6

7 8

9

10

- ¹H nmr (400 MHz, CDCl₃) 2.13 (s, 3H) 3.78 (s, 3H) 11
- 6.83 (d, 2H, 9 Hz) 7.38 (d, 2H, 9 Hz). 13 C nmr (100 12
- MHz, CDCl₃) 24.66 (CH₃) 55.85 (CH₃) 114.49 (CH) 13
- 122.37 (CH) 131.41 (Q) 156.82 (Q) 168.79 (Q). EI+ 14
- 165.1 (71%, M⁺) 123.1 (70%, [M-Ac]⁺) 108.1 (100%, 15
- [NH₂PhO]⁺) C₉H₁₁NO₂ Calc. 165.0790 Found 165.0789. 16

17

N-(3-Acetyl-4-hydroxy-phenyl)-acetamide 18

- 1 To a stirring suspension of N-(4-methoxy-phenyl)-
- 2 acetamide (5.253 g, 32 mmol) and acetyl chloride
- 3 (6.6 ml, 93 mmol, 2.9 equ) in dichloromethane (55
- 4 ml) was added aluminium trichloride (14.55 g, 109
- 5 mmol, 3.4 equ) in portions over 90 minutes. The
- 6 reaction was then heated to reflux for 4.5 hours
- 7 and cooled overnight. The mixture was poured onto
- 8 ice then extracted into dichloromethane (5x), dried
- 9 (MgSO₄) and concentrated in vacuo to give N-(3-
- 10 acetyl-4-hydroxy-phenyl)-acetamide (5.336 g, 87 %)
- 11 as a pale green solid.

- 14 ¹H nmr (400 MHz, CDCl₃) 2.19 (s, 3H) 2.63 (s, 3H)
- 15 6.94 (d, 1H, 9 Hz) 7.12 (brs, 1H, NH) 7.33 (dd, 1H,
- 16 2.6+9 Hz) 8.17 (d, 1H, 2.6 Hz) 12.12 (s, 1H). 13 C
- 17 nmr (100 MHz, CDCl₃) 24.71 (CH₃) 27.16 (CH₃) 119.08
- 18 (CH) 119.60 (Q) 122.94 (CH) 129.58 (CH) 159.62 (Q)
- 19 168.86 (Q) 204.84 (Q). EI+ 193.1 (100%, M⁺) 151.1
- 20 (91%, $[M-Ac]^+$) $C_{10}H_{11}NO_3$ Calc. 193.0739 Found
- 21 193.0740.

- 23 <u>1-(5-Amino-2-hydroxy-phenyl)-ethanone</u>
- 24 A suspension of N-(3-acetyl-4-hydroxy-phenyl)-
- 25 acetamide (1.029 g, 5.3 mmol) in 15% HCl (1.5 ml,
- 26 6.2 mmol, 1.2 equ) was heated to reflux for 40
- 27 minutes, then cooled and neutralised with 10%
- 28 aqueous ammonia. The precipitated solid was
- 29 collected by filtration as 1-(5-amino-2-hydroxy-
- 30 phenyl)-ethanone (0.677 g, 84%) a green solid.

1

2

 $_{4}$ 1 H nmr (400 MHz, CDCl₃) 2.58 (s, 3H) 3.47 (brs, 2H)

5 6.83 (d, 1H, 8.8 Hz) 6.91 (dd, 1H, 2.8+8.8 Hz) 7.02

6 (d, 1H, 2.8 Hz). ¹³C nmr (100 MHz, CDCl₃) 27.12

7 (CH₃) 115.71 (CH) 119.40 (CH) 119.87 (Q) 125.737

8 (CH) 138.40 (Q) 156.03 (Q) 204.48 (Q). EI+ 151.1

9 (100%, M⁺) C₈H₉NO₂ Calc. 151.0633 Found 151.0632.

10

11 1-(5-Iodo-2-hydroxy-phenyl)-ethanone (52)

12 To a stirring solution of 1-(5-amino-2-hydroxy-

phenyl)-ethanone (6.856 g,46 mmol) in 98% sulfuric

14 acid (24 ml) and water (19 ml) was added sodium

15 nitrite (3.30 g, 48 mmol, 1.05 equ) in water (5.5

16 ml). The reaction was stirred for 35 minutes, then

17 sulfuric acid (4 ml), copper powder (0.17 g, 0.3

18 mmol, 0.06 equ) and potassium iodide (8.80 g, 53

19 mmol, 1.16 equ) in water (5.5 ml) added. The

20 mixture was then heated slowly to 65°C and

21 maintained at 65°C for 2 hours. The reaction was

22 then cooled, water (25 ml) and sodium hydrogen

23 carbonate added. More water was added, then

24 extracted into a mixture of ethyl acetate and

25 dichloromethane, then ethyl acetate (2x). The

26 combined organic layers were washed with brine then

27 concentrated in vacuo. This mixture was then taken

28 up in ethyl acetate and 2 M HCl, filtered and the

29 organic layer dried (MgSO₄) and concentrated in

30 vacuo to give 1-(5-iodo-2-hydroxy-phenyl)-ethanone

75

1 52 (1.339 g, 39 %) as a purple oil. This was then

2 used in the next reaction.

3

<u>4</u> 5

- 6 1-(2-Hydroxy-5-iodo-phenyl)-3-(4-benzyloxy-3,5-
- 7 dimethoxy-phenyl)-propenone (54)
- 8 To a stirring solution of 1-(5-iodo-2-hydroxy-
- 9 phenyl)-ethanone 52 (4.243 g, 16 mmol) and 4-
- 10 benzyloxy-3,5-dimethoxy benzaldehyde (4.51 g, 17
- 11 mmol, 1.02 equ) in ethanol (100 ml) was added
- 12 potassium hydroxide (1.839 g, 33 mmol, 2.03 equ).
- 13 The reaction mixture was stirred for 191 hours then
- 14 acidified with 6 M HCl and diluted with water and
- 15 brine. The mixture was extracted into ethyl acetate
- 16 (3x). The combined organic layers were then washed
- 17 with brine, dried (MgSO₄) and concentrated in vacuo
- 18 to give a black oil. This was taken up in ethanol
- 19 (50 ml), potassium hydroxide (1.97 g) added and
- 20 stirred for 169 hours. The reaction was then
- 21 acidified with 6 M HCl and diluted with water then
- 22 extracted into ethyl acetate (3x) washed with
- 23 brine, dried (MgSO₄) and concentrated in vacuo to
- 24 give a black foam. Recrystallisation (ethanol)
- 25 yielded 1-(2-hydroxy-5-iodo-phenyl)-3-(4-benzyloxy-
- 26 3,5-dimethoxy-phenyl)-propenone 54 (4.122 g, 49 %).

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2 EI+ 516 (31%, M⁺) 425 (32%, [M-Bn]⁺) 91 (100%, Bn⁺)

3 C₂₄H₂₁IO₅ Calc. 516.0434 Found 516.0435.

4

1

- 5 3-Hydroxy-6-iodo-2-(4-benzyloxy-3,5-dimethoxy-
- 6 phenyl)-chromen-4-one (56)
- 7 To a stirring solution of 1-(2-hydroxy-5-iodo-
- 8 phenyl)-3-(4-benzyloxy-3,5-dimethoxy-phenyl)-
- 9 propenone **54** (4.155 g, 8 mmol) in methanol (80 ml)
- 10 and 16 % aqueous sodium hydroxide solution (10 ml,
- 11 40 mmol, 5 equ) at 0°C was added 15 % aqueous
- 12 hydrogen peroxide (10 ml, 44 mmol, 5.5 equ)
- 13 dropwise. The solution was stirred at 0°C for ten
- 14 minutes then sealed and placed in a refrigerator
- 15 for 16 hours. The reaction was then acidified (6 M
- 16 HCl), diluted with water and extracted into
- 17 dichloromethane (3x). The organic layer was then
- 18 washed with sodium hydrogen carbonate solution and
- 19 brine, dried (MgSO₄) and concentrated to give a
- 20 brown solid. Recrystallisation (ethanol) yielded 3-
- 21 hydroxy-6-iodo-2-(4-benzyloxy-3,5-dimethoxy-
- 22 phenyl)-chromen-4-one 56 (2.106 g, 49%) as a grey
- 23 solid.

1 2

- 1 H nmr (400 MHz, CDCl₃) 3.93 (s, 6H) 5.12 (s, 2H)
- 4 7.00 (brs, 1H) 7.25-7.38 (m, 5H) 7.49-7.51 (m, 3H)
- 5 7.95 (dd, 1H, 2.2+8.9 Hz) 8.58 (s, 1H). 13C nmr
- 6 (100 MHz, CDCl₃) 56.73 (CH₃) 75.71 (CH₂) 105.92 (CH)
- 7 120.94 (Q) 123.00 (Q) 128.39 (CH) 128.65 (CH)
- 8 128.86 (CH) 134.89 (Q) 138.10 (Q) 142.43 (Q) 154.10
- 9 (Q) 155.02 (Q). EI+ 530.4 (31%, M⁺) 439.3 (91%, [M-
- 10 Bn] +) 91.1 (100%, Bn+) C24H19IO6 Calc. 530.0226 Found
- 11 530.0226.

- 13 3-Hydroxy-6-decyl-2-(4-benzyloxy-3,5-dimethoxy-
- 14 phenyl)-chromen-4-one (58)
- 15 To a stirring solution of 1-decene (0.189 g, 1.3
- 16 mmol, 1.4 eq) in tetrahydrofuran (2 ml) under argon
- 17 was added 9-BBN in tetrahydrofuran (0.5M, 2.8 ml,
- 18 1.4 mmol, 1.5 eq). The reaction was stirred for 8
- 19 hours then 3-hydroxy-6-iodo-2-(4-benzyloxy-3,5-
- 20 dimethoxy-phenyl)-chromen-4-one 56 (0.501 g, 0.9
- 21 mmol) in tetrahydrofuran (5 ml), 3M NaOH solution
- 22 (1.26 ml) and dichloropalladium(dppf) (0.021 g,
- 23 0.03 mmol, 0.03 eq) were added and the reaction
- 24 heated to reflux for 15 hours. The reaction was
- 25 then guenched with water and diethyl ether and
- 26 acidified (6 M HCl). The organic layer was
- 27 collected and the aqueous layer extracted with
- 28 diethyl ether (2x). The combined organic layers

1 were washed with brine, dried (MgSO₄) and

- 2 concentrated in vacuo to give a red oil. This was
- 3 passed through a short plug of silica, eluting with
- 4 ethyl acetate to give 3-hydroxy-6-decyl-2-(4-
- 5 benzyloxy-3,5-dimethoxy-phenyl)-chromen-4-one
- 6 58(0.369 g, 72%) as a red oil.

7

8

- 10 6-Decyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-
- 11 chromen-4-one (11g)
- 12 To a stirring solution of 3-hydroxy-6-decyl-2-(4-
- 13 benzyloxy-3,5-dimethoxy-phenyl)-chromen-4-one
- 14 (0.369 q, 0.7 mmol) in dichloromethane (20 ml)
- 15 under Ar at 0°C was added boron tribromide in
- 16 dichloromethane (1.0M, 3.4 ml, 3.4 mmol, 5 equ).
- 17 The mixture was warmed to room temperature and then
- 18 stirred for 15 hours. Methanol (10 ml) was then
- 19 added. The reaction was heated to reflux for 1
- 20 hour, then concentrated in vacuo to give a brown
- 21 solid. Water (25 ml) was added and then extracted
- 22 into ethyl acetate (3x). The organic layer was
- 23 washed with brine then dried (MgSO₄) and
- 24 concentrated in vacuo to give 11g (0.318 g, 110 %)
- 25 as a brown oil.

- 27 The substituted flavonol 9d was further purified by
- 28 treatment with acetic anhydride (6 eq.) and N,N-

- 1 dimethyl-4-aminopyridine (0.05 eq.) in pyridine (60
- 2 eq.). When the reaction was complete, this was
- 3 diluted with ethyl acetate and washed with dilute
- 4 hydrochloric acid and saturated sodium bicarbonate
- 5 solution. The organic solution was then dried
- 6 (MgSO₄) and concentrated to give the crude
- 7 tetraacetate derivative. Recrystallization from
- 8 methanol gave the pure substituted tetraacetate,
- 9 which was deprotected by heating in methanol (ca.
- 10 0.05M) containing catalytic concentrated
- 11 hydrochloric acid for 1 hour. Dilution with water
- 12 gave the substituted flavonol no. 11g as a fine
- 13 yellow precipitate that was collected by filtration
- 14 or extraction into ethyl acetate.

16

- 19 ¹H nmr (400 MHz, CD₃SOCD₃) 1.25 (t, 3H, 6.4 Hz)
- 20 1.62-1.72 (m, 14H) 1.99-2.04 (m, 2H) 3.13 (t, 2H,
- 21 7.5 Hz) 7.72 (s, 2H) 7.98-8.04 (m, 2H) 8.28 (s, 1H)
- 22 9.21 (s, 1H) 9.61 (s, 3H). ¹³C nmr (100 MHz,
- 23 D₃CSOCD₃) 14.28 (CH₃) 22.43 (CH₂) 28.86 (CH₂) 29.01
- 24 (CH₂) 29.15 (CH₂) 29.15 (CH₂) 29.30 (CH₂) 31.20
- 25 (CH₂) 31.62 (CH₂) 34.75 (CH₂) 107.59 (CH) 118.27
- 26 (CH) 121.31 (Q) 121.54 (Q) 123.50 (CH) 134.30 (CH)
- 27 136.04 (Q) 138.30 (Q) 138.97 (Q) 146.06 (Q) 146.34

```
(Q) 153.14 (Q) 172.69 (Q). FAB+ 427.4 (100%,
 1
     [M+H]^+) C_{25}H_{31}O_6 calc. 427.2122 found 427.2123.
 2
 3
    The reaction is summarised in the following scheme:
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Br₂, CHCl₃

i) AcCl, AlCl₃, CH₂Cl₂ (87%)ii) HCl_(m) (84%)

iii) NaNO₂, H₂SO₄ KI, Cu, H₂O (39%) x

52 $R^2 = H, X = I$ 53 $R^2 = Et, X = Br$

(76%)

OH

56 R^2 = H, X = I 49% 57 R^2 = Et, X = Br 40% 31 KOH, EtOH

OMe

OBn

OMe

OMe

OMe

A R² = H, X = I 49%

55 R² = Et, X = Br 19%

1-decene or 1-octene

58 R¹ = ${}^{n}C_{10}H_{21}$, R² = H72% 59 R¹ = ${}^{n}C_{8}H_{17}$, R² = Et i) BBr₃, CH₂Cl₂

R² OH OH

11g R¹ = ${}^{n}C_{10}H_{21}$, R² = H 84% 12 R¹ = ${}^{n}C_{8}H_{17}$, R² = Et 100% over next two steps

1

2

1 Example 12

2

- 3 A dual chain flavonoid was prepared as described
- 4 below:

5

- 6 1-(5-Bromo-4-ethyl-2-hydroxy-phenyl)-ethanone (53)
- 7 To a stirring solution of 18 (prepared as described
- 8 in Example 1) (1.002 g, 6.1 mmol) in chloroform (10
- 9 ml) under argon at -12°C was added bromine (0.32
- 10 ml, 6.2 mmol, 1.02 equ) in chloroform (5 ml) over
- 11 20 minutes. The reaction was stirred at -12°C for
- 12 50 minutes, then poured into water (20 ml). The
- 13 organic layer was washed with water (10 ml), 10%
- 14 sodium thiosulfate (2x 10 ml), and water (10 ml),
- 15 dried (MgSO₄) then concentrated in vacuo to give 1-
- 16 (5-bromo-4-ethyl-2-hydroxy-phenyl)-ethanone 53
- 17 (1.132 g, 76 %) as a brown solid.

18

19 20

- 21 ¹H nmr (400 MHz, CDCl₃). ¹³C nmr (100 MHz, CDCl₃).
- 22 EI+ 242(+244) (16%, M⁺) 227(+229) (40%, [M-Me]⁺)
- 23 $C_{10}H_{11}BrO_2$ calc. 241.9942 + 243.9923 found 241.9941
- 24 + 243.9916.

- 26 1-(5-Bromo-4-ethyl-2-hydroxy-phenyl)-3-(4-
- 27 benzyloxy-3,5-dimethoxy-phenyl)-propenone (55)
- 28 To a stirring solution of 1-(5-bromo-4-ethyl-2-
- 29 hydroxy-phenyl)-ethanone 53 (1.132 g, 4.7 mmol) and
- 30 4-benzyloxy-3,5-dimethoxy benzaldehyde 31 (0.918 g,

- 1 4.7 mmol, 1.0 equ) in ethanol (30 ml) was added
- 2 potassium hydroxide (0.545 g, 9.7 mmol, 2.1 equ).
- 3 The reaction mixture was stirred for 26 hours then
- 4 · acidified with 10% HCl and diluted with water. The
- 5 mixture was extracted into ethyl acetate (4x). The
- 6 combined organic layers were then washed with
- 7 brine, 10 % sodium bisulfite solution, saturated
- 8 aqueous sodium bicarbonate and brine again. The
- 9 organic layer was then dried (MgSO₄) and
- 10 concentrated in vacuo to give a brown oil.
- 11 Recrystallisation (ethanol) yielded 1-(5-bromo-4-
- ethyl-2-hydroxy-phenyl)-3-(4-benzyloxy-3,5-
- dimethoxy-phenyl)-propenone 55 (0.368 g, 19 %).

- 17 ¹H nmr (400 MHz, CDCl₃) 1.26 (t, 3H, 7.5 Hz) 2.76
- 18 (q, 2H, 7.5 Hz) 3.92 (s, 6H) 5.10 (s, 2H) 6.88 (s,
- 19 2H) 6.94 (s, 1H) 7.28-7.42 (m, 3H) 7.48 (dd, 1H,
- 20 1.4+6.7 Hz) 7.85 (d, 1H, 15 Hz) 8.03 (s, 1H) 12.78
- 21 (s, 1H). 13 C nmr (100 MHz, CDCl₃) 13.89 (CH₃), 30.25
- 22 (CH₂), 56.74 (CH₃) 75.53 (CH₂) 106.61 (CH) 113.24
- 23 (Q) 119.01 (CH) 119.54 (CH) 119.89 (Q) 128.41 (CH)
- 24 128.61 (CH) 128.86 (CH) 130.38 (Q) 133.16 (CH)
- 25 137.81 (Q) 140.31 (Q) 146.77 (CH) 152.75 (Q) 154.25
- 26 (Q) 163.24 (Q) 192.47 (Q). EI+ 496(+498) (18%, M⁺)
- 27 405(+407) (35%, [M-Bn]⁺) 91.1 (100%, Bn⁺) C₂₆H₂₅BrO₅

- 1 calc. 496.0855 + 498.0869 found 496.0884 +
- 2 498.0863.

- 4 6-Bromo-7-ethyl-3-hydroxy-2-(4-benzyloxy-3,5-
- 5 dimethoxy-phenyl)-chromen-4-one (57)
- 6 To a stirring solution of 1-(5-bromo-4-ethyl-2-
- 7 hydroxy-phenyl) -3-(4-benzyloxy-3,5-dimethoxy-
- 8 phenyl)-propenone 55 (0.238 g, 0.5 mmol) in
- 9 methanol (10 ml) and 16 % aqueous sodium hydroxide
- 10 solution (0.6 ml, 2.4 mmol, 5 equ) at 0°C was added
- 11 15 % aqueous hydrogen peroxide (0.6 ml, 2.6 mmol,
- 12 5.5 equ) dropwise. The solution was stirred at 0°C
- 13 for ten minutes then sealed and placed in a
- 14 refrigerator for 115 hours. The reaction was then
- 15 acidified (2 M HCl) and extracted into
- 16 dichloromethane (2x). The organic layer was then
- 17 washed with brine, dried (MgSO₄) and concentrated
- 18 to give a yellow foam. Recrystallisation (ethanol)
- 19 yielded 6-bromo-7-ethyl-3-hydroxy-2-(4-benzyloxy-
- 20 3,5-dimethoxy-phenyl)-chromen-4-one 57 (0.097 g,
- 21 40%) as a yellow solid.

- 24 ¹H nmr (400 MHz, CDCl₃) 1.34 (t, 3H, 7.5 Hz) 2.90
- 25 (q, 2H, 7.5 Hz) 3.94 (s, 6H) 5.12 (s, 2H) 6.99 (s,
- 26 1H) 6.99 (s, 1H) 7.25-7.38 (m, 4H) 7.46-7.52 (m,
- 27 4H) 8.40 (s, 1H). ¹³C nmr (100 MHz, CDCl₃) 14.03

1 (CH₃), 30.23 (CH₂), 56.70 (CH₃) 75.47 (CH₂) 105.82

- 2 (CH) 118.60 (CH) 120.19 (Q) 120.92 (Q) 126.50 (Q)
- 3 128.36 (CH) 128.60 (CH) 129.08 (CH) 137.95 (Q)
- 4 138.52 (Q) 139.35 (Q) 145.20 (Q) 150.03 (Q) 153.88
- 5 (Q) 154.66 (Q) 172.32 (Q).

6

- 7 7-Ethyl-3-hydroxy-6-octyl-2-(4-benzyloxy-3,5-
- 8 dimethoxy-phenyl)-chromen-4-one (59)
- 9 To a stirring solution of 1-octene (0.032 g, 0.3
- 10 mmol, 1.4 eq) in tetrahydrofuran (1 ml) under argon
- 11 at 0°C was added 9-BBN in tetrahydrofuran (0.5M,
- 12 0.6 ml, 0.3 mmol, 1.5 eq). The reaction was stirred
- 13 for 7 hours then 6-bromo-7-ethyl-3-hydroxy-2-(4-
- benzyloxy-3,5-dimethoxy-phenyl)-chromen-4-one 57
- 15 (0.102 g, 0.2 mmol) in tetrahydrofuran (4 ml), 3M
- 16 NaOH solution (0.2 ml) and dichloropalladium(dppf)
- 17 (0.005 g, 0.006 mmol, 0.03 eq) were added and the
- 18 reaction heated to reflux for 15 hours. The
- 19 reaction was then quenched with water and diethyl
- 20 ether and acidified (6 M HCl). The organic layer
- 21 was collected and the aqueous layer extracted with
- 22 dichloromethane. The combined organic layers were
- 23 washed with brine, dried (MgSO4) and concentrated
- 24 in vacuo to give a red oil.

25 26

86

- 1 7-Ethyl-3-hydroxy-6-octyl-2-(3,4,5-trihydroxyphenyl) -chromen-4-one (12) 2 3 To a stirring solution of 7-ethyl-3-hydroxy-6octyl-2-(4-benzyloxy-3,5-dimethoxy-phenyl)-chromen-4 4-one **59** (0.125 g, 0.2 mmol) in dichloromethane (10 5 ml) under Ar at 0°C was added boron tribromide in 6 dichloromethane (1.0M, 1.2 ml, 1.2 mmol, 5.2 equ). 7 The mixture was warmed to room temperature and then 8 stirred for 21 hours. Methanol (5 ml) was then 9 added. The reaction was heated to reflux for 2 10 hours, then concentrated in vacuo to give a brown 11 solid. Water (10 ml) was added then extracted into 12 ethyl acetate (3x). The organic layer was washed 13 with brine then dried (MgSO₄) and concentrated in 14 vacuo to give 12 (0.088 g, 100% over 2 steps) as a 15 green solid. 16 17 The substituted flavonol 12 was further purified by 18 treatment with acetic anhydride (6 eq.) and N, N-19 dimethyl-4-aminopyridine (0.05 eq.) in pyridine (60 20 When the reaction was complete, this was 21 diluted with ethyl acetate and washed with dilute 22 hydrochloric acid and saturated sodium bicarbonate 23 solution. The organic solution was then dried 24 (MqSO₄) and concentrated to give the crude 25 tetraacetate derivative. Recrystallization from 26 methanol gave the pure substituted tetraacetate, 27 which was deprotected by heating in methanol (ca. 28 0.05M) containing catalytic concentrated 29

30

31

hydrochloric acid for 1 hour. Dilution with water

gave the substituted flavonol 12 as a fine yellow

87

1 precipitate that was collected by filtration or

2 extraction into ethyl acetate.

3

4 5

6 ¹H nmr (400 MHz, CD₃SOCD₃) 0.91 (m, 3H) 1.29-1.40

7 (m, 13H) 1.61-1.65 (m, 2H) 2.75-2.88 (m, 4H) 7.35

8 (s, 2H) 7.49 (s, 1H) 7.86 (s, 1H) 8.81 (s, 1H)

9 9.16-9.30 (m, 3H). ¹³C nmr (100 MHz, D₃CSOCD₃) 14.30

10 (CH₃) 14.70 (CH₃) 22.43 (CH₂) 25.33 (CH₂) 29.00

11 (CH₂) 29.18 (CH₂) 29.34 (CH₂) 30.71 (CH₂) 31.62

12 (CH₂) 31.69 (CH₂) 108.53 (CH) 116.80 (CH) 119.40

13 (Q) 121.66 (Q) 123.96 (CH) 135.91 (Q) 137.42 (Q)

14 138.14 (Q) 146.06 (Q) 146.06 (Q) 148.83 (Q) 153.38

15 (Q) 172.52 (Q). FAB+ 447.4 (100%, $[M+H]^+$) $C_{25}H_{31}O_6$

16 calc. 427.2121 found 427.2125.

17

18 The reaction can be summarised in the following

19 scheme:

2 An alternative scheme was employed to produce 7-

3 alkyl-flavonols. Briefly, the alkyl chain was

4 introduced by Suzuki cross-coupling prior to the

5 construction of the flavonoid by Baker-Venkataraman

6 rearrangement.

7

i) MeOCH₂CN, ZnCl₂ HCl_(g) Et₂O (47%) ii) Tf₂O, 2,6-lutidine

CH₂Cl₂, 0°C (87%)

TrO OH OMe

1-decene, 9-BBN (Ph₃P)₄Pd K₃PO₄, THF, 65°C

EDCl, DMAP

←——

CH₂Cl₂

ArCO₂H

65 Ar = 2,4,5-(MeO)₃C₆H₂ 68% 66 Ar = 2,3,4-(MeO)₃C₆H₂ 58%

OMe

Me₃SiOTf, CH₂Cl₂

67 Ar = 2,4,5-(MeO)₃C₆H₂ 88% 68 Ar = 2,3,4-(MeO)₃C₆H₂ 60%

"C10H21"

69 Ar = 2,4,5-(MeO)₃C₆H₂ 69%. 70 Ar = 2,3,4-(MeO)₃C₆H₂ 87%

BBr₃, CH₂Cl₂

13g Ar = 2,4,5-(HO)₃C₆H₂ 98% 15g Ar = 2,3,4-(HO)₃C₆H₂ 98%

2 Example 13

1

5

6

3
4 1-(2',4'-dihydroxy)-phenyl-2-methoxy ethanone

90

- 1 Resorcinol 62 (1.78 g, 16.14 mmol, 1.2 eq),
- 2 methoxyacetonitrile (1.00 ml, 13.44 mmol) and zinc
- 3 chloride (366 mg, 2.69 mmol, 0.2 eq) were placed in
- 4 a three necked round bottomed flask and dissolved
- 5 in dry diethyl ether (10 ml) under argon. The
- 6 solution was cooled to 0°C and the argon inlet
- 7 replaced with a calcium chloride drying tube. Dry
- 8 hydrochloric acid was bubbled through the solution
- 9 for 2 hours. The resulting precipitate was filtered
- 10 off and washed with ether (10 ml). The
- 11 hydrochloride salt was dissolved in water (10 ml)
- 12 and heated under reflux for 30 minites After
- 13 cooling the resulting solid was filtered off and
- 14 washed with water (10 ml) and dried under vacuum to
- 15 give the acetophenone (1.16 g, 47%). m.p. 108-
- 16 110°C.

- 18 $\delta_{\rm H}$ (400 MHz: D-6 DMSO): 3.35 (3H, s, OCH₃), 4.66
- 19 (2H, s, OCH₂), 6.29 (1H, d, J 2.3 Hz, H-3'), 6.36
- 20 (1H, dd, J 2.3 Hz and 8.8 Hz, H-5'), 7.68 (1H, d, J
- 21 8.8 Hz, H-6'), 10.59 (1H, s, OH), 11.92 (1H, s,
- 22 OH).
- 23 $\delta_{\rm C}$ (100 MHz: D-6 DMSO): 58.89 (CH₃), 74.68 (CH₂),
- 24 102.80 (CH), 108.55 (CH), 111.99 (C), 132.26 (CH),
- 25 163.77 (C), 164.95 (C), 199.52 (C).
- 26 m/z (EI): 182.1 (M⁺, 10%), 137.0 (100).
- 27 Found: 182.0581 $C_9H_{10}O_4$ requires (M⁺) 182.0579.
- 28 Found: C, 59.43%; H, 5.50%. C₉H₁₀O₄ requires C,
- 29 59.34%, H 5.53%.
- 30 v_{max} (golden gate)/cm⁻¹: 3361 (OH), 1633 (C=O).
- 31 R_f silica EtOAc 0.56

91

1

4

2 1-(2'-hydroxy-4'-trifluoromethanesulfonyloxy)-

3 phenyl-2-methoxy ethanone (63)

5 Trifluoromethanesulfonic anhydride (2.55 ml, 15.54

6 mmol, 1.0 eq) was added slowly to a solution of 1-

7 (2',4'-dihydroxy)-phenyl-2-methoxy ethanone (2.83

8 g, 15.54 mmol) and 2,6-lutidine (1.81 ml, 15.54

9 mmol, 1.05 eq) in dry dichloromethane (50 ml)

10 cooled to 0°C and under an atmosphere of argon.

11 After 1 hour the solution was diluted with

12 dichloromethane (100 ml) and washed with 1 M

13. hydrochloric acid (100 ml). The organic layer was

14 re-extracted with dichloromethane (50 ml) and the

15 combined organics washed with 1 M hydrochloric acid

16 (100 ml). The organics were then dried over

17 magnesium sulfate and concentrated under vacuum to

18 give the triflate as a purple oil suitably pure for

19 the next step (4.31 g, 87%). The product was

20 contaminated with some ditriflate.

21

22 δ_{H} (400 MHz: CDCl₃): 3.53 (3H, s, OCH₃), 4.68 (2H,

23 s, CH₂), 6.84 (1H, dd, J 2.5 and 8.9 Hz, H-5), 6.94

24 (1H, d, J 2.5 Hz, H-3), 7.85 (1H, d, J 8.9 Hz, H-

25 6), 12.14 (1H, s, OH).

26

27 1-(2'-hydroxy-4'-decyl)-phenyl-2-methoxy ethanone

28 (64)

92

2 9-BBN (0.5 M solution in THF, 152.6 ml, 76.29 mmol,

3 1.05 eq) was added to decene (14.44 ml, 76.29 mmol,

4 1.05 eq) at room teperature under argon. The

5 solution was then stirred at room temperature for 6

6 h. After this time K₃PO₄ (23.19 g, 108.99 mmol, 1.5

7 eq), $Pd(Ph_3P)_4$ (2.10 g, 1.81 mmol, 0.025 eq) were

8 added followed by a solution of 63 (22.81 g, 72.66

9 mmol) in dry THF (100 ml). The reaction mixture was

10 then heated to 65°C under argon overnight.

11 After cooling the solution was acidified to pH 1

12 and extracted into EtOAc (300ml). The aqueous layer

13 was re-extracted with EtOAc (200ml) and the

14 combined organics washed with H₂O (2 x 500ml) and

15 brine (500 ml). The organic layer was dried over

16 magnesium sulphate and concentrated under vacuum.

17 The resulting residue was purified by column

18 chromatography on silica eluting dichloromethane to

19 give the acetophenone as a pale yellow solid (6.79

20 g, 30%). m.p. <25°C.

21

22 $\delta_{\rm H}$ (400 MHz: CDCl₃): 0.88 (3H, t, J 6.7 Hz, CH₂CH₃),

23 1.22-1.31 (14H, m, $7 \times CH_2$), 1.57-1.65 (2H, m,

24 ArCH₂CH₂), 2.61 (2H, t, J 7.5 Hz, ArCH₂CH₂), 3.53

25 (3H, s, OCH₃), 4.71 (2H, s, OCH₂), 6.73 (1H, dd, J

26 1.6 Hz and 8.2 Hz, H-5), 6.83 (1H, d, J 1.4 Hz, H-

27 3), 7.58 (1H, d, J 8.0 Hz, H-5), 11.98 (1H, s, OH).

28 $\delta_{\rm C}$ (100 MHz: CDCl₃): 14.05 (CH₃), 22.61 (CH₂), 29.16

29 (CH₂), 29.25 (CH₂), 29.37 (CH₂), 29.47 (CH₂), 29.53

30 (CH₂), 30.53 (CH₂), 31.83 (CH₂), 36.20 (CH₂), 59.48

- 1 (CH₃), 74.19 (CH₂), 115.48 (C), 117.93 (CH), 119.69
- 2 (CH), 128.53 (CH), 153.33 (C), 162.52 (C), 200.78
- 3 (C).
- 4 m/z (EI): 306.1 (M⁺, 10%), 261.1 (100), 147.0 (25),
- 5 45.0 (30).
- 6 Found: $306.2194 C_{19}H_{30}O_3$ requires (M⁺) 306.2195.
- 7 Found: C, 74.74%; H, 10.03%. C₁₉H₃₀O₃ requires C,
- 8 74.47%, H 9.87%.
- 9 v_{max} (thin film)/cm⁻¹: 3039 (OH), 2925 (CH₂), 1648
- 10 (C=O).
- 11 R_f Silica DCM 0.26

12

- 13 1-(2'-[2'',4'',5''-trimethoxy-benzoyloxy]-4'-decyl-
- 14 phenyl) -2-methoxy-ethanone (65)

- 16 EDCI (860 mg, 4.49 mmol, 1.5 eq) was added to a
- 17 solution of 64 (916 mg, 2.99 mmol, 1.0 eq),
- 18 trimethoxybenzoic acid (634 mg, 2.99 mmol, 1.0 eq)
- 19 and DMAP (36 mg, 0.30 mmol, 0.1 eq) in dry
- 20 dichloromethane (10 ml) under argon at room
- 21 temperature. The resulting solution was stirred
- 22 overnight. The reaction mixture was then diluted
- 23 with DCM (20 ml) and washed with brine (50 ml). The
- 24 aqueous layer was re-extracted with DCM (20 ml) and
- 25 the combined organics washed with brine (50 ml).
- 26 The organic layer was then dried over magnesium
- 27 sulfate and concentrated under vacuum.
- 28 The resulting residue was purified by column
- 29 chromatography on silica eluting EtOAc: Hexane 2:1

1 to give the ester as a pale yellow solid (1.01 g,

2 68%). m.p. 80-81°C.

3

- 4 $\delta_{\rm H}$ (400 MHz: CDCl₃): 0.88 (3H, t, J 6.8 Hz, CH₂CH₃),
- 5 1.26-1.31 (14H, m, 7 x CH₂), 1.60-1.67 (2H, m,
- 6 ArCH2CH2), 2.66 (2H, t, J 7.6 Hz, ArCH2CH2), 3.38
- 7 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.94 (3H, s,
- 8 OCH₃), 3.97 (3H, s, OCH₃), 4.56 (2H, s, OCH₂), 6.58
- 9 (1H, s, H-5[^]), 7.08 (1H, d, J 1.2 Hz, H-3[^]), 7.15
- 10 (1H, dd, J 1.2 Hz and 8.0 Hz, H-5), 7.65 (1H, s,
- 11 H-6'), 7.80 (1H, d, J 8.0 Hz, H-6').
 - 12 $\delta_{\rm C}$ (100 MHz: CDCl₃): 14.05 (CH₃), 22.61 (CH₂), 29.21
 - 13 (CH₂), 29.24 (CH₂), 29.36 (CH₂), 29.47 (CH₂), 29.53
 - 14 (CH₂), 30.75 (CH₂), 31.82 (CH₂), 35.74 (CH₂), 56.09
 - 15 (CH₃), 56.41 (CH₃), 56.81 (CH₃), 59.19 (CH₃), 77.18
 - 16 (CH₂), 97.35 (CH), 108.85 (C), 114.77 (CH), 123.79
 - 17 (CH), 125.97 (CH), 126.53 (C), 129.69 (CH), 142.71
 - 18 (C), 149.79 (2 x C), 154.69 (C), 156.79 (C), 163.39
 - 19 (C), 196.20 (C).
 - 20 m/z (EI): 500.3 (M⁺, 5%), 261.1 (10), 195.1 (100).
 - 21 Found: $500.2776 C_{29}H_{40}O_7$ requires (M^{\dagger}) 500.2774.
 - 22 v_{max} (golden gate)/cm⁻¹: 2913 (CH₂), 1747 (CO₂), 1685
 - 23 (C=O).
 - 24 R_f 0.31 silica (EtOAc:Hexane 2:1)

25

- 26 Synthesis of 1-(2'-hydroxy-4'-decylphenyl)-2-
- 27 methoxy-3-(2'',4'',5'-trimethoxyphenyl)-propan-1,3-
- 28 dione (67)

95

- 1 Lithium hexamethyldisilylazide (1.0 M solution in
- 2 THF) (4.88 ml, 4.88 mmol, 3.0 eq) was added
- 3 dropwise to a solution of 65 (814 mg, 1.63 mmol,
- 4 1.0 eg) in dry THF (6 ml) cooled to -20°C and under
- 5 argon. After 1 h. the reaction was quench with
- 6 saturated NaHCO3 solution (30 ml) and extracted in
- 7 EtOAc (50 ml). The aqueous phase was re-extracted
- 8 with EtOAc (20 ml) and the combined organics washed
- 9 with brine $(2 \times 100 \text{ ml})$. The organic phase was then
- 10 dried over magnesium sulfate and concentrated under
- 11 vacuum to give the diketone as an off white solid
- 12 suitably pure for the next step (717 mg, 88%). m.p.
- 13 99-101°C.

- 15 $\delta_{\rm H}$ (400 MHz: CDCl₃): 0.88 (3H, t, J 6.8 Hz, CH₂CH₃),
- 16 1.26-1.31 (14H, m, 7 x CH₂), 1.58-1.63 (2H, m,
- 17 ArCH₂CH₂), 2.62 (2H; t, J 7.5 Hz, ArCH₂CH₂), 3.48
- 18 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), 3.91 (3H, s,
- 19 OCH₃), 3.92 (3H, s, OCH₃), 5.90 (1H, s, H-2), 6.37
- 20 (1H, s, H-3⁻), 6.80-6.82 (2H, m, H-3⁻ and H-5⁻),
- 21 7.62 (1H, s, H-6'), 7.78 (1H, d, J 8.1 Hz, H-6'),
- 22 11.65 (1H, s, OH).
- 23 δ_{C} (100 MHz: CDCl₃): 14.09 (CH₃), 22.65 (CH₂), 29.23
- 24 (CH₂), 29.29 (CH₂), 29.42 (CH₂), 29.52 (CH₂), 29.57
- 25 (CH_2) , 30.55 (CH_2) , 31.87 (CH_2) , 36.26 (CH_2) , 55.29
- 26 (CH₃), 56.14 (CH₃), 56.24 (CH₃), 58.89 (CH₃), 86.83
- 27 (CH), 95.70 (CH), 112.08 (C), 116.31 (C), 116.47
- 28 (C), 117.83 (CH), 119.94 (CH), 130.45 (CH), 138.10
- 29 (C), 143.68 (C), 153.29 (C), 154.92 (C), 163.15
- 30 (C), 191.92 (C), 198.68 (C).
- 31 m/z (EI): 500.3 (M⁺, 1%), 261.1 (10), 195.1 (100).
- 32 Found: $500.2775 C_{29}H_{40}O_7$ requires (M) 500.2774.

1 v_{max} (golden gate)/cm⁻¹: 2915 (CH₂), 1664 (C=0), 1631

2 (C=0).

3 R_f silica (EtOAc:Hexane 1:1) 0.41

4

5 Synthesis of 3,2',4',5'-tetramethoxy-7-decyl-flavone (69)

6

7

8 TMSOTf (0.245 ml, 1.35 mmol, 1.1 eq) was added

9 slowly to a solution of 67 (614 mg, 1.23 mmol) in

10 dry DCM (4 ml) at room temperature under argon. The

11 yellow solution was then stirred for 1 h and then

12 quenched with saturated NaHCO3 solution (30 ml) and

13 extracted into DCM (20 ml). The aqueous layer was

14 re-extracted with DCM (20 ml) and the combined

15 organics washed with brine (50 ml). The organic

16 layer was then dried over magnesium sulfate and

17 concentrated under vacuum. The residue was purified

18 by column chromatography on silica eluting

19 EtOAc:hexane 1:1 to give the flavone as a viscous

20 yellow oil (409 mg, 69%).

21

22 $\delta_{\rm H}$ (400 MHz: CDCl₃): 0.88 (3H, t, J 6.8 Hz, CH₂CH₃),

23 1.24-1.32 (14H, m, $7 \times CH_2$), 1.63-1.70 (2H, m,

24 ArCH₂CH₂), 2.72 (2H, t, J 7.5 Hz, ArCH₂CH₂), 3.82

25 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 3.87 (3H, s,

26 OCH₃), 3.97 (3H, s, OCH₃), 6.64 (1H, s, H-3¹), 7.00

27 (1H, s, H-6'), 7.21 (1H, dd, J 1.3 Hz and 8.2 Hz,

28 H-6), 7.26 (1H, d, J 1.3 Hz, H-8), 8.18 (1H, d, J

29 8.2 Hz, H-5).

- 1 $\delta_{\rm C}$ (100 MHz: CDCl₃): 14.06 (CH₃), 22.63 (CH₂), 29.15
- 2 (CH₂), 29.26 (CH₂), 29.39 (CH₂), 29.49 (CH₂), 29.54
- 3 (CH₂), 30.87 (CH₂), 31.84 (CH₂), 35.98 (CH₂), 56.07
- 4 (CH₃), 56.56 (CH₃), 56.69 (CH₃), 60.28 (CH₃), 97.58
- 5 (CH), 111.42 (C), 113.62 (CH), 117.08 (CH), 122.29
- 6 (C), 125.39 (CH), 125.54 (CH), 141.73 (C), 142.93
- 7 (C), 149.39 (C), 151.68 (C), 152.38 (C), 155.41
- 8 (C), 155.86 (C), 174.75 (C).
- 9 m/z (EI): 482.2 (M⁺, 60%), 467.2 (75), 451.2 (100).
- 10 Found: $482.2672 \, C_{29}H_{38}O_6$ requires (M⁺) 482.2668.
- 11 v_{max} (thin film)/cm⁻¹: 2927 (CH₂), 1644 (C=0).
- 12 R_f Silica (EtOAc:hexane 1:1) 0.31

13

14 Synthesis of 3,2',4',5'-tetrahydroxy-7-decyl-flavone (13g)

15

ОН ОН

- 17 Boron tribromide (1.0 M solution in DCM) (4.0 ml,
- 18 4.06 mmol, 5.0 eq) was added slowly to a solution
- 19 of 69 (392 mg, 0.81 mmol) in dry DCM (3 ml) at 0°C.
- 20 under argon. The solution was then stirred
- 21 overnight and then methanol (5 ml) added slowly.
- 22 The solution was heated under reflux for 30 min.
- 23 then concentrated under vacuum. Water (20 ml) was
- 24 added to the residue and the flask placed in a
- 25 sonic bath for 5 min. The resulting fine
- 26 precipitate was filtered off and washed with water
- 27 (10 ml) then freeze dried to give the flavonol as a
- 28 red/brown amorphous solid (338 mg, 98%). m.p.
- 29 decomp > 90°C.

1. δ_{H} (400 MHz: D-6 DMSO): 0.84 (3H, t, J 6.7 Hz, 2 CH_2CH_3), 1.22-1.28 (14H, m, 7 x CH_2), 1.60-1.64 (2H, 3 m, $ArCH_2CH_2$), 2.72 (2H, t, J 7.5 Hz, $ArCH_2CH_2$), 6.43 4 (1H, s, H-3), 6.87 (1H, s, H-6), 7.28 (1H, d, J 5 8.2 Hz, H-6), 7.39 (1H, s, H-8), 8.00 (1H, d, J 8.2 6 7 Hz, H-5). δ_{C} (100 MHz: D-6 DMSO): 14.28 (CH₃), 22.42 (CH₂), 8 28.91 (CH₂), 29.01 (CH₂), 29.13 (CH₂), 29.30 (CH₂), 9 $29.31 \text{ (CH}_2)$, $30.70 \text{ (CH}_2)$, $31.62 \text{ (CH}_2)$, $35.37 \text{ (CH}_2)$, 10 104.55 (CH), 108.65 (C), 116.77 (CH), 117.45 (CH), 11 120.26 (C), 124.94 (CH), 125.38 (CH), 138.07 (C), 12 138.28 (C), 148.14 (C), 148.90 (C), 149.05 (C), 13 149.10 (C), 155.43 (C), 172.59 (C). 14 m/z (FAB): 427.4 ((M+H)⁺, 100%). 15 Found: $427.2120 C_{25}H_{31}O_6$ requires $((M+H)^+)$ 427.2121. 16 v_{max} (golden gate)/cm $^{-1}$: 3226 (OH), 2919 (CH $_2$), 1558 17 (C=0). 18 19 20 21 22 Example 14 23 24 1-(2'-[2'',3'',4''-trimethoxy-benzoyloxy]-4'-decyl-25 phenyl) -2-methoxy-ethanone 66 26

27

EDCI (914 mg, 4.77 mmol, 1.5 eq) was added to a 28

solution of 64 (produced as described in Example 29

99

- 1 13) (973 mg, 3.18 mmol, 1.0 eq), trimethoxybenzoic
- 2 acid (675 mg, 3.18 mmol, 1.0 eq) and DMAP (39 mg,
- 3 0.32 mmol, 0.1 eq) in dry dichloromethane (10 ml)
- 4 under argon at room temperature. The resulting
- 5 solution was stirred overnight. The reaction
- 6 mixture was then diluted with DCM (20 ml) and
- 7 washed with brine (50 ml). The aqueous layer was
- 8 re-extracted with DCM (20 ml) and the combined
- 9 organics washed with brine (50 ml). The organic
- 10 layer was then dried over magnesium sulfate and
- 11 concentrated under vacuum.
- 12 The resulting residue was purified by column
- 13 chromatography on silica eluting EtOAc:Hexane 1:1
- 14 to give the ester as a colourless oil (927 mg,
- 15 58%).

- 17 $\delta_{\rm H}$ (400 MHz: CDCl₃): 0.88 (3H, t, J 6.8 Hz, CH₂CH₃),
- 18 1.25-1.31 (14H, m, 7 x CH₂), 1.60-1.68 (2H, m,
- 19 ArCH₂CH₂), 2.67 (2H, t, J 7.6 Hz, ArCH₂CH₂), 3.39
- 20 (3H, s, OCH₃), 3.91 (3H, s, OCH₃), 3.95 (3H, s,
- 21 OCH₃), 3.98 (3H, s, OCH₃), 4.55 (2H, s, OCH₂), 6.78
- 22 (1H, d, J 8.8 Hz, H-5), 7.07 (1H, d, J 1.2 Hz, H-
- 23 3), 7.16 (1H, dd, J 1.2 Hz and 8.0 Hz, H-5), 7.77
- 24 (1H, d, J 8.0 Hz, H-6), 7.88 (1H, d, J 8.8 Hz, H-
- 25 6``).
- 26 $\delta_{\rm C}$ (100 MHz: CDCl₃): 14.03 (CH₃), 22.59 (CH₂), 29.18
- 27 (CH₂), 29.23 (CH₂), 29.34 (CH₂), 29.45 (CH₂), 29.50
- 28 (CH_2) , 30.70 (CH_2) , 31.81 (CH_2) , 35.70 (CH_2) , 56.10
- 29 (CH₃), 59.17 (CH₃), 60.98 (CH₃), 61.84 (CH₃), 76.87
- 30 (CH₂), 107.06 (CH), 116.46 (C), 123.76 (CH), 126.03
- 31 (CH), 126.39 (C), 127.83 (CH), 129.62 (CH), 143.06

100

1 (C), 149.61 (C), 149.92 (C), 155.50 (C), 158.00

2 (C), 163.25 (C), 196.00 (C).

3

- 4 m/z (EI): 500.3 (M^{+} , 5%), 261.1 (15), 195.1 (100).
- 5 Found: $500.2772 C_{29}H_{40}O_7$ requires (M⁺) 500.2774.
- 6 v_{max} (thin film)/cm⁻¹: 2927 (CH₂), 1743 (CO₂), 1702
- 7 (C=0).
- 8 R_f Silica (EtOAc:Hexane 1:1) 0.30

9

- 10 Synthesis of 1-(2'-hydroxy-4'-decylphenyl)-2-
- methoxy-3-(2'',3'',4''-trimethoxyphenyl)-propan-
- 12 1,3-dione (68)

13

- 14 Lithium hexamethyldisilylazide (1.0 M solution in
- 15 THF) (3.84 ml, 3.84 mmol, 3.0 eq) was added
- 16 dropwise to a solution of 66 (641 mg, 1.28 mmol,
- 17 1.0 eq) in dry THF (5 ml) cooled to -20°C and under
- 18 argon. After 1 h. the reaction was quench with
- 19 saturated NaHCO3 solution (30 ml) and extracted in
- 20 EtOAc (50 ml). The aqueous phase was re-extracted
- 21 with EtOAc (20 ml) and the combined organics washed
- 22 with brine (2 x 100 ml). The organic phase was then
- 23 dried over magnesium sulfate and concentrated under
- 24 vacuum. The resulting bright yellow oil was
- 25 purified by column chromatography on silica eluting
- 26 EtOAc: Hexane 1:2 to give the diketone as a yellow
- 27 solid (387 mg, 60%). m.p. 60-62°C.

- 29 $\delta_{\rm H}$ (400 MHz: CDCl₃): 0.88 (3H, t, J 6.8 Hz, CH₂CH₃),
- 30 1.26-1.31 (14H, m, $7 \times CH_2$), 1.58-1.63 (2H, m,

101

- 1 ArCH₂CH₂), 2.60 (2H, t, J 7.5 Hz, ArCH₂CH₂), 3.57
- 2 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 3.80 (3H, s,
- 3 OCH₃), 3.91 (3H, s, OCH₃), 5.58 (1H, s, H-2), 6.73
- 4 (1H, d, J 8.8 Hz, H-5), 6.76 (1H, dd, J 1.6 Hz
- 5 and 8.4 Hz, H-5), 6.80 (1H, d, J 1.6 Hz, H-3),
- 6 7.66 (1H, d, J 8.8 Hz, H-6), 7.81 (1H, d, J 8.4
- 7 Hz, H-6'), 11.72 (1H, s, OH).
- 8 $\delta_{\rm C}$ (100 MHz: CDCl₃): 14.08 (CH₃), 22.65 (CH₂), 29.24
- 9 (CH₂), 29.29 (CH₂), 29.41 (CH₂), 29.51 (CH₂), 29.56
- 10 (CH₂), 30.50 (CH₂), 31.86 (CH₂), 36.28 (CH₂), 56.13
- 11 (CH₃), 58.77 (CH₃), 60.80 (CH₃), 61.01 (CH₃), 88.19
- 12 (CH), 107.14 (CH), 116.20 (C), 117.76 (CH), 119.90
- 13 (CH), 123.04 (C), 126.21 (CH), 130.79 (CH), 141.29
- 14 (C), 153.59 (C), 153.66 (C), 158.36 (C), 163.28
- 15 (C), 193.54 (C), 198.84 (C).
- 16 m/z (EI): 500.3 (M⁺, 1%), 261.1 (5), 195.1 (100).
- 17 Found: $500.2773 C_{29}H_{40}O_7$ requires (M⁺) 500.2774.
- 18 v_{max} (thin film)/cm⁻¹: 3403 (OH), 2927 (CH₂), 1685
- 19 (C=O), 1637 (C=O).
- 20 R_f silica (EtOAc:Hexane 1:2) 0.29

21

22 Synthesis of 3,2',3',4'-tetramethoxy-7-decyl-flavone (70)

23

- 26 TMSOTf (0.12 ml, 0.66 mmol, 1.1 eq) was added
- 27 slowly to a solution of 68 (299 mg, 0.59 mmol) in
- 28 dry DCM (2 ml) at room temperature under argon. The
- 29 yellow solution was then stirred for 1 h and then

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- quenched with saturated NaHCO3 solution (20 ml) and 1
- extracted into DCM (20 ml). The aqueous layer was 2
- re-extracted with DCM (20 ml) and the combined 3
- organics washed with brine (50 ml). The organic 4
- layer was then dried over magnesium sulfate and 5
- concentrated under vacuum to give the flavone as a 6
- viscous yellow oil (251 mg, 87%). 7

8

- $\delta_{\rm H}$ (400 MHz: CDCl₃): 0.88 (3H, t, J 6.8 Hz, CH₂CH₃), 9
- 1.26-1.31 (14H, m, 7 x CH₂), 1.62-1.70 (2H, m, 10
- $ArCH_2CH_2$), 2.72 (2H, t, J 7.5 Hz, $ArCH_2CH_2$), 3.80 11
- 12 $(3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.94 (3H, s,$
- 13 OCH_3), 3.95 (3H, s, OCH_3), 6.78 (1H, d, J 8.7 Hz,
- 14 H-5), 7.19-7.25 (3H, m, H-6,8 and 6), 8.18 (1H,
- d, J 8.2 Hz, H-5). 15
- $\delta_{\rm C}$ (100 MHz: CDCl₃): 14.06 (CH₃), 22.63 (CH₂), 29.15 16
- 17 (CH₂), 29.39 (CH₂), 29.49 (CH₂), 29.54 (CH₂), 29.54
- (CH₂), 30.89 (CH₂), 31.84 (CH₂), 35.99 (CH₂), 56.07 18
- (CH_3) , 60.40 (CH_3) , 60.88 (CH_3) , 61.48 (CH_3) , 107.00 19
- (CH), 117.03 (CH), 118.04 (C), 122.47 (C), 125.40 20
- (CH), 125.46 (CH), 125.60 (CH), 141.69 (C), 142.37 21
- (C), 149.55 (C), 152.36 (C), 155.61 (C), 155.75 22
- (C), 155.61 (C), 174.76 (C). 23
- m/z (EI): 482.2 (M⁺, 60%), 467.2 (75), 451.2 (100). 24
- Found: $482.2666 \, C_{29}H_{38}O_6 \, \text{requires} \, (M^{\dagger}) \, 482.2669.$ 25
- v_{max} (thin film)/cm⁻¹: 2929 (CH₂), 1621 (C=0). 26
- R_f silica (EtOAc:Hexane 1:1) 0.44 27

28

29 Example 15

30

1-(2-Allyloxy-phenyl)-ethanone 31

103

1 To a stirring suspension of 2-hydroxyacetophenone

2 72 (5 ml, 42 mmol) and potassium carbonate (6.516

3 g, 47 mmol, 1.1 equ) in acetone (30 ml) was added

4 allyl bromide (4 ml, 46 mmol, 1.1 equ). The

5 reaction was heated to reflux for 20 hours. The

6 reaction was then concentrated in vacuo, taken up

7 in water and extracted into ethyl acetate (2x). The

8 organic layer was then dried (MgSO₄) and

9 concentrated in vacuo to give an yellow oil. This

10 was taken up in diethyl ether, washed with 1M

11 potassium hydroxide then dried (MgSO₄) and

12 concentrated in vacuo to give 1-(2-allyloxy-

phenyl)-ethanone (3.70 g, 51 %) as a pale yellow

14 oil.

15

16 ¹H nmr (400 MHz, CDCl₃) 2.64 (s, 3H) 4.65 (td, 2H,

17 1.5+5.3 Hz) 5.32 (ddd, 1H, 1.4+1.3+10.5 Hz) 5.44

18 (ddd, 1H, 1.5+1.6+17 Hz) 6.04-6.14 (m, 1H) 6.93-

19 7.02 (m, 2H) 7.44 (td, 1H, 1.9+7.3 Hz) 7.73 (dd,

20 1H, 1.8+7.7 Hz). ¹³C nmr (100 MHz, CDCl₃) 32.38

21 (CH₃) 69.78 (CH₂) 113.15 (CH) 118.58 (CH₂) 121.17

22 (CH) 130.81 (CH) 133.02 (CH) 133.90 (CH) 158.29 (Q)

23 200.32 (Q). EI+ 176.1 (21%, M⁺) 161.1 (100%, [M-

24 Me]⁺) 121.0 (100%, [M-(Allyl+Me)]⁺) C₁₁H₁₂O₂ Calc.

25 176.0837 Found 176.0838.

26

27 1-(3-Ally1-2-hydroxy-phenyl)-ethanone (73)

28 1-(2-Allyloxy-phenyl)-ethanone (2.518 g, 14 mmol)

29 was heated to 200°C for 44 hours to give 1-(3-

1 allyl-2-hydroxy-phenyl)-ethanone 73 (2.518 g,

2 100%).

4 ¹H nmr (400 MHz, CDCl₃) 2.63 (s, 3H) 3.43 (d, 2H,

5 6.6 Hz) 5.06-5.11 (m, 1H) 5.95-6.06 (m, 1H) 6.85

6 (t, 1H, 7.7 Hz) 7.36 (d, 1H, 7.2 Hz) 7.62 (dd, 1H,

7 1.4+8 Hz). ¹³C nmr (100 MHz, CDCl₃) 27.17 (CH₃)

8 33.80 (CH₂) 116.39 (CH₂) 118.81 (CH) 119.63 (Q)

9 129.20 (CH) 129.79 (Q) 136.49 (CH) 136.87 (CH)

10 160.81 (Q) 205.15 (Q). EI+ 176.1 (90%, M⁺) 161.1

11 $(100\%, [M-Me]^+)$ $C_{11}H_{12}O_2$ Calc. 176.0837 Found

12 176.0837.

13

3

14 1-(2-Hydroxy-3-allyl-phenyl)-3-(2,4,5-trimethoxy-

15 phenyl)-propenone (74)

16 To a stirring suspension of 1-(3-allyl-2-hydroxy-

17 phenyl)-ethanone **73** (1.779 g, 27 mmol) and 2,4,5-

18 trimethoxy benzaldehyde (5.89 g, 30 mmol, 1.1 equ)

19 in ethanol (50 ml) was added potassium hydroxide

20 (3.23 g, 58 mmol, 2.1 equ). The reaction mixture

21 was stirred for 191 hours then acidified (2 M HCl)

22 and extracted with ethyl acetate (3x). The combined

23 organic layers were then washed with water and

24 brine then dried (MgSO₄) and concentrated in vacuo

25 to give 1-(2-hydroxy-3-allyl-phenyl)-3-(2,4,5-

26 trimethoxy-phenyl)-propenone **74** (11.165 g, 116 %)

27 as an orange solid.

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1 2

3 ¹H nmr (400 MHz, CDCl₃) 3.47 (d, 2H, 6.6 Hz) 3.92

4 (s, 3H) 3.94 (s, 3H) 3.96 (s, 3H) 5.08-5.14 (m, 2H)

5 5.99-6.10 (m, 1H) 6.53 (s, 1H) 6.88 (t, 1H, 7.7 Hz)

6 7.13 (s, 1H) 7.36 (d, 1H, 6.5 Hz) 7.63 (d, 1H, 15.5

7 Hz) 7.82 (dd, 1H, 1.4+8.1 Hz) 8.21 (d, 1H, 15.5 Hz)

8 13.43 (s, 1H). ¹³C nmr (100 MHz, CDCl₃) 33.94 (CH₂)

9 56.49 (CH₃) 56.73 (CH₃) 57.08 (CH₃) 97.12 (CH)

10 112.20 (CH) 115.69 (Q) 116.31 (CH₂) 118.49 (CH)

11 118.57 (CH) 120.19 (Q) 128.04 (CH) 129.80 (Q)

12 136.29 (CH) 136.68 (CH) 138.51 (Q) 141.12 (CH)

13 143.71 (Q) 153.33 (Q) 155.46 (CH) 161.97 (Q) 194.66

14 (Q). EI+ 354.4 (69%, M^{+}) 323.3 (100%, $[M-OMe]^{+}$)

15 C₂₁H₂₂O₅ Calc. 354.1467 Found 354.1468.

16

17 8-Allyl-3-hydroxy-2-(2,4,5-trimethoxy-phenyl)-

18 chromen-4-one (75)

19 To a stirring solution of 1-(2-hydroxy-3-allyl-

phenyl) -3-(2,4,5-trimethoxy-phenyl)-propenone 74

21 (11.15 g, 31 mmol) in methanol (300 ml) and 16 %

22 aqueous sodium hydroxide solution (37 ml, 148 mmol,

23 4.7 equ) at 0°C was added 15 % aqueous hydrogen

24 peroxide (37 ml, 163 mmol, 5.2 equ) dropwise. The

25 solution was stirred at 0°C for ten minutes then

26 sealed and placed in a refrigerator for 23 hours.

27 The reaction was then acidified (2 M HCl) and

28 extracted into chloroform (3x). The organic layer

29 was then washed with brine, dried (MgSO4) and

106

- 1 concentrated to give an orange solid. This was
- 2 taken up in methanol (300 ml) and 16 % aqueous
- 3 sodium hydroxide solution (37 ml, 148 mmol, 4.7
- 4 equ) at 0°C, then 15 % aqueous hydrogen peroxide
- 5 (37 ml, 163 mmol, 5.2 equ) was added and the
- 6 solution stirred at 0°C for the 5 minutes then
- 7 sealed and place in a refrigerator for 18 hours.
- 8 The reaction was then acidified (2 M HCl) and
- 9 extracted into dichloromethane (3x). The organic
- 10 layer was then dried (MgSO₄) and concentrated to
- 11 give an orange solid. Recrystallisation (ethanol)
- 12 yielded 8-allyl-3-hydroxy-2-(2,4,5-trimethoxy-
- 13 phenyl)-chromen-4-one 75 (4.815 g, 42%) as a yellow
- 14 solid.

15

- 18 ¹H nmr (400 MHz, CDCl₃) 3.66 (d, 2H, 6.5 Hz) 3.89
- 19 (s, 6H) 3.98 (s, 3H) 5.07-5.12 (m, 2H) 6.00-6.11
- 20 (m, 1H) 6.53 (brs, 1H) 6.67 (s, 1H) 7.19 (s, 1H)
- 21 7.34 (t, 1H, 7.7 Hz) 7.53 (dd, 1H, 1.4+7.1 Hz) 8.15
- 22 (dd, 1H, 1.6+8.0 Hz). 13 C nmr (100 MHz, CDCl₃) 34.15
- 23 (CH₂) 56.51 (CH₃) 56.94 (CH₃) 57.14 (CH₃) 98.19 (CH)
- 24 111.37 (Q) 114.00 (CH) 116.98 (CH₂) 121.74 (Q)
- 25 124.05 (CH) 124.50 (CH) 130.13 (Q) 133.72 (CH)
- 26 135.97 (CH) 138.75 (Q) 143.49 (Q) 145.88 (Q) 152.32
- 27 (Q) 152.94 (Q) 154.26 (Q) 173.76 (Q). EI+ 368.4
- 28 (100%, M^{+}) 373.3 (87%, [M-OMe]⁺) $C_{21}H_{20}O_{6}$ Calc.
- 29 368.1260 Found 368.1259.

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1 Tetradec-7-ene 2 A mixture of 1-octene (7.15 g, 64 mmol) and Grubbs' 3 catalyst (0.030 g, 0.04 mmol, 0.0006 equ) was 4 stirred under a static vacuum for 15 hours, then 5 passed through a plug of silica eluting with 6 hexane. Concentration gave tetradec-7-ene (4.982 g, 7 80%) as a colourless liquid. 8 9 C₆H₁₃\ 10 11 ¹H nmr (400 MHz, CDCl₃) 0.86-0.90 (m, 6H) 1.21-1.41 12 (m, 16H) 1.94-2.04 (m, 4H) 5.31-5.43 (m, 2H). ¹³C 13 nmr (100 MHz, CDCl₃) 14.48 (CH₃) 23.04 (CH₂) 27.60 14 (CH₂) 29.23 (CH₂) 29.38 (CH₂) 30.02 (CH₂) 30.13 15 (CH₂) 32.15 (CH₂) 32.17 (CH₂) 33.00 (CH₂) 130.28 16 (CH) 130.75 (CH). EI+ 196 (9%, M^+) $C_{14}H_{28}$ Calc. 17 196.2191 Found 196.2191. 18 19 3-Hydroxy-8-non-2-enyl-2-(2,4,5-trimethoxy-phenyl)-20 chromen-4-one (76) 21 To a stirring solution of tetradec-7-ene (0.539 g, 22 2.75 mmol, 2.1 equ) and Grubbs' first generation 23 catalyst (0.029 g, 0.04 mmol, 0.03 equ) in 24 dichloromethane (13.5 ml) under argon was added 8-25 ally1-3-hydroxy-2-(2,4,5-trimethoxy-phenyl)-26 chromen-4-one 75 (0.479 g, 1.3 mmol). The reaction 27 was heated to reflux for 5.5 hours then 28 concentrated in vacuo to give a brown solid. 29 30 Recrystallisation (ethanol) yielded 3-hydroxy-8-

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non-2-enyl-2-(2,4,5-trimethoxy-phenyl)-chromen-4-

2 one 76 (0.258 g, 26%) as an lilac solid.

3

4 5

6 ¹H nmr (400 MHz, CDCl₃) 0.84-0.90 (m, 3H) 1.21-1.47

7 (m, 8H) 1.97-2.02 (m, 2H) 3.58-3.71 (m, 2H) 3.75-

8 4.07 (m, 11H) 5.37-5.40 (m, 0.25H) 5.49-5.66 (m,

9 1H) 5.75-5.78 (m, 0.75H) 6.50-6.54 (m, 2H) 6.64 (d,

10 1H, 19.2 Hz) 7.09 (s, 0.25H) 7.18 (d, 0.75H, 11Hz)

11 7:24-7.35 (m, 1H) 7.40-7.53 (m, 1H) 8.08-8.14 (m,

12 1H).

13

14 3-Hydroxy-8-nonyl-2-(2,4,5-trimethoxy-phenyl)-

15 chromen-4-one (77)

16 A stirring suspension of 3-hydroxy-8-non-2-enyl-2-

17 (2,4,5-trimethoxy-phenyl)-chromen-4-one 76 (0.258

18 g, 0.6 mmol) and 10% palladium on carbon (0.024 g)

19 in ethyl acetate (30 ml) was placed under an

20 atmosphere of hydrogen for 43 hours. The reaction

21 was filtered through celite, the residue washed

22 with ethyl acetate and the combined filtrates

23 concentrated in vacuo to give a grey solid.

24 Recrystallisation (petrol:ethyl acetate 2:1)

yielded 3-hydroxy-8-nonyl-2-(2,4,5-trimethoxy-

26 phenyl)-chromen-4-one 77 (0.212g, 82 %) as an off-

27 white solid.

109

1 2

 1 H nmr (400 MHz, CDCl₃) 0.87 (t, 3H, 6.7 Hz) 1.18-

4 1.39 (m, 12H) 1.68-1.72 (m, 2H) 2.88 (t, 2H, 7.6

5 Hz) 3.88 (s, 3H) 3.89 (s, 3H) 3.98 (s, 3H) 6.53

6 (brs, 1H) 6.67 (s, 1H) 7.18 (s, 1H) 7.32 (t, 1H,

7 7.7 Hz) 7.50 (d, 1H, 6.2 Hz) 8.12 (d, 1H, 6.6 Hz).

8

9 8-Nonyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-

10 chromen-4-one (14g)

11 To a stirring solution of 3-hydroxy-8-nonyl-2-

12 (2,4,5-trimethoxy-phenyl)-chromen-4-one 77 (0.209

13 q, 0.5 mmol) in dichloromethane (15 ml) under Ar at

14 0°C was added boron tribromide in dichloromethane

15 (1.0M, 2.3 ml, 2.3 mmol, 5 equ). The mixture was

16 warmed to room temperature and then stirred for 18

17 hours. Methanol (7 ml) was then added. The reaction

18 was heated to reflux for 2 hours, then concentrated

19 in vacuo to give a red oil. Water (25 ml) was added

20 then extracted into ethyl acetate (3x). The organic

21 layer was washed with brine then dried (MgSO₄) and

22 concentrated in vacuo to give 14g (0.203 g, 107 %)

23 as a brown solid.

24

25 The substituted flavonol 14g was further purified

26 by treatment with acetic anhydride (6 eq.) and N, N-

27 dimethyl-4-aminopyridine (0.05 eq.) in pyridine (60

28 eq.). When the reaction was complete, this was

29 diluted with ethyl acetate and washed with dilute

110

1 hydrochloric acid and saturated sodium bicarbonate

- 2 solution. The organic solution was then dried
- 3 (MgSO₄) and concentrated to give the crude
- 4 tetraacetate derivative. Recrystallization from
- 5 methanol gave the pure substituted tetraacetate,
- 6 which was deprotected by heating in methanol (ca.
- 7 0.05M) containing catalytic concentrated
- 8 hydrochloric acid for 1 hour. Dilution with water
- 9 gave the substituted flavonol 14g as a fine yellow
- 10 precipitate that was collected by filtration or
- 11 extraction into ethyl acetate.

12

13 14

- 15 1 H nmr (400 MHz, CD₃SOCD₃) 0.83 (t, 3H, 6.7 Hz)
- 16 1.17-1.29 (m, 12H) 1.61-1.65 (m, 2H) 2.84 (t, 2H,
- 17 7.4 Hz) 7.01 (s, 1H) 7.37 (t, 1H, 1.6 Hz) 7.60 (d,
- 18 1H, 7.1 Hz) 7.96 (dd, 1H, 1.4+8.0 Hz) 9.45 (s, 1H)
- 19 9.65 (s, 1H). 13 C nmr (100 MHz, D_3 CSOC D_3) 14.31
- 20 (CH₃) 22.42 (CH₂) 28.94 (CH₂) 28.98 (CH₂) 29.02
- 21 (CH₂) 29.07 (CH₂) 29.26 (CH₂) 29.43 (CH₂) 31.61
- 22 (CH₂) 101.53 (Q) 109.72 (Q) 114.69 (CH) 122.27 (Q)
- 23 122.78 (CH) 124.31 (CH) 132.25 (Q) 133.39 (CH)
- 24 138.79 (Q) 146.10 (Q) 146.88 (Q) 153.54 (Q) 173.09
- 25 (Q). EI+ 491.3 (14%) 413.4 (1%, [M+H]*) 85.6
- 26 (100%).

- 28 The reactions are summarised in the following
- 29 scheme:

1

2

1 Example 15

2

3 A 9-C alkyl chain compound was prepared as

4 described in Example 6. The reaction is summarised

5 by the scheme given below:

6

7

8 Example 16

9

10 The following reaction was carried out.

1 2

Example 17

4

- 5 Within a biological system where a number of
- 6 polyphenols may be present at similar
- 7 concentrations, antioxidant efficacy may be
- 8 predominantly governed by reaction kinetics rather
- 9 than stoichiometry. Consequently, the antioxidant
- 10 potential of thirteen flavonoids and vitamin E were
- 11 assessed and their kinetic and stochiometric
- 12 reduction of a synthetic radical using stopped-flow

1 electron spin resonance (ESR) spectroscopy has been

2 compared. The radical used was galvinoxyl (Galv-

3 0°), $(2,6-di-tert-butyl-\alpha-(3,5-di-tert-butyl-4-oxo-$

4 2,5-cyclohexadien-1-ylidene)-p-tolyloxy) shown

5 below:

6

7 Galvinoxyl is resonance-stabilised and sterically-

8 protected, and so displays little self-reactivity

9 in solution, is reduced by H-atom transfer

10 reactions in the presence of phenolic compounds.

11

Galv-0° + Phenol-OH ← Galv-OH + phenol-0°

13

14 The process is governed by the O-H bond

15 dissociation enthalpy of the donor. Galvinoxyl has

16 a well-defined ESR spectrum and this property was

17 used to calculate second order rate constants, as

18 well as establishing stoichiometry, for the

19 reaction with phenolic compounds.

20 21

Materials

22

23 Tamarixetin and myricetin-3',4',5'-trimethylether

24 were purchased from Indofine Chemical Co.

25 (Somerville, USA). The remaining flavonoids, $d-\alpha$ -

26 tocopherol and galvinoxyl (2,6-di-tert-butyl-a-

27 (3,5-di-tert-butyl-4-oxo-2,5-cyclohexadien-1-

1	ylidene)-p-tolyloxy) were purchased from Sigma-
2	Aldrich Chemical Co. (Poole, Dorset, UK) and
3	ethanol (>99.7%) from BDH Laboratory Supplies
4	(Poole, Dorset, UK). Reagents were used without
5	further purification.
6	
7	Methods
8	
9	Kinetic Measurements
10	
11	Ethanolic solutions of flavonoid (0.2 mM) and
12	galvinoxyl (0.2 mM) were de-oxygenated under a
13	stream of nitrogen gas. Aliquots (6 ml) were
14	transferred to Hamilton gas-tight syringes (10 ml)
15	coupled to a pneumatic ram and connected to a two-
16	stream ESR quartz flow-cell. In situ reaction at
17	20°C \pm 2°C between the flavonoid and galvinoxyl was
18	initiated by rapidly evacuating the syringes.
19	Spectra and decay curves were obtained on a Bruker
20	ECS 106 spectrometer operating at ca. 9.5 GHz (X-
21	band) and equipped with a TM_{110} cavity. Decay
22	curves were obtained by operating in timesweep mode
23	with the static field set at the resonance maximum
24	of the galvinoxyl signal.
25	
26	Stoichiometric Measurements
27	
28	Ethanolic solutions of flavonoids (0.1 mM) were
29	prepared. Aliquots (3 ml) of an ethanolic
30	galvinoxyl solution (0.5 mM) were mixed with an
31	equal volume of flavonoid solution then transferred
32	to an ESR quartz cell. The spectra and reaction

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stoichiometry were evaluated. In brief, the 1 spectra of the unreacted galvinoxyl were obtained 5 2 minutes from mixing, by which time equilibration 3 was complete. The galvinoxyl concentrations 4 remaining were calculated by double integration of 5 the signal and comparing with the control 6 experiment where ethanol was added to the 7 galvinoxyl solution instead of flavonoid solution. 8 9 10 Results 11 The ESR spectrum of galvinoxyl in an ethanolic solution consists of a doublet of quintets (Figure 12 1) which arise from the interaction of the unpaired 13 electron spin with the nuclear spins of the proton 14 on the central carbon and the four equivalent 15 aromatic ring protons. In the presence of a 16 hydrogen donating compound, such as quercetin, the 17 resonances decay as reduction of the radical 18 proceeds. Data from all the decay curves gave a 19 good linear fit to the second-order integrated rate 20 expression, with the average correlation 21 coefficient for each set of replicates being 22 greater than 0.970. However, there were marked 23 differences between the flavonoids in the kinetics 24 of the reduction of the galvinoxyl free radical. 25 Myricetin and morin were, by far, the fastest to 26 react whereas hesperitin and apigenin showed little 27 reactivity. Ranking of reaction rates as second 28

order rate constants was: myricetin > morin >

quercetin > fisetin ≈ catechin > kaempferol ≈

luteolin > rutin > taxifolin > tamarixetin >

myricetin-3',4',5'-trimethylether > datiscetin >

29

30

31

32

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1	galangin > hesperitin \approx apigenin. Reaction rates
2	of eight of the flavonoids were greater than that
3	for vitamin E.
4	
5	The stoichiometry of the reaction of these
6	compounds with the galvinoxyl free radical was
7	determined by adding the flavonoid, or vitamin E,
8	to an excess of the radical and allowing the
9	reaction to proceed to the endpoint. This resulted
10	in a ranking of antioxidant capacity which differed
11	from the kinetic ranking i.e. myricetin > fisetin >
12	quercetin ≈ luteolin > rutin > catechin > taxifolin
13	> kaempferol ≈ morin > datiscetin > tamarixetin >
14	myricetin-3',4',5'-trimethylether ≈ galangin >
15	hesperitin > apigenin. In particular, the reaction
16	of morin with galvinoxyl had the second fastest
17	rate of all compounds, but was only ranked eighth
. 18	equal in terms of the number of radicals reduced.
19	Seven of the flavonoids had a greater reaction
20	stoichiometry than vitamin E. Datiscetin,
21	galangin, hesperitin and apigenin were the four
22	lowest ranked of all the compounds in both the
23	kinetic and stoichiometric measurements of
24	antioxidant potential.
25	
26	Discussion
27	
28	A large number of natural phenolic compounds in
29	fruit, vegetables, tea and wines have antioxidant
30	activity due to their hydrogen donor activity and
31	their ability to complex transition metal ions. In

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addition to the location and total number of 1 hydroxyl groups, the solubility of the phenolics in 2 the test medium may significantly affect their 3 ability to act as antioxidants. For example, 4 antioxidant activity of flavonoids in lard appears 5 to be related to the number of ortho-dihydroxy 6 groupings in the A and B-rings whereas a lack of 7 conjugation between the B and C-rings is a major 8 influence in aqueous media. The kinetic 9 measurements in the present Application indicate 10 that reactivity of the flavonoids with galvinoxyl 11 in an organic medium is highly-dependent on the 12 configuration of OH groups on the B and C-ring 13 14 systems. 15 Galangin, which has no OH groups on the B-ring 16 reacted only very slowly. However, addition of an 17 OH group to the 4' position (position 12 in Formula 18 1) (kaempferol) increased the rate by a factor of 19 about 70. The presence of an OH group on the C-20 ring was also important because the reaction with 21 apigenin, which has the 4'-OH group (position 12 in 22 Formula 1), but no OH at the 3-position on the C-23 ring, was slow, whereas the rate of reaction with 24 kaempferol, which has both of these hydroxyl 25 26 groups, was almost 250-fold greater. 27 The importance of further addition of hydroxyl 28 groups to the B-ring was illustrated when comparing 29 luteolin to apigenin. Luteolin is apigenin with an 30 OH added ortho- to the 4'-OH (position 12 in 31

Formula 1). The presence of this catechol function

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- 1 imparts significant activity in its own right as 2 luteolin, which lacks the 3-OH, reacted with 3 galvinoxyl at a rate similar to kaempferol.
- 4 However, the ability of the 3-OH to enhance
- 5 reactivity was demonstrated by the doubling of the
- 6 rate constant in quercetin compared with luteolin.
- 7 The difference in rate constant between quercetin
- 8 and rutin also illustrated the influence that a
- 9 group at the 3-position has on the kinetics of the
- 10 reaction of flavonoids with galvinoxyl.

- 12 Substitution of the 3-OH of quercetin by an ether-
- 13 linked sugar group (rutin) caused an approximate 3-
- 14 fold decrease in the rate of reaction, although the
- 15 rate constant was still greater than those for
- 16 apigenin, hesperitin, galangin, datiscetin,
- 17 taxifolin and vitamin E. By comparison with
- 18 luteolin, the increased reaction rate of quercetin
- 19 may be ascribed to electron donation by the 3-OH
- 20 through the resonance effect, as the B- and C-rings
- 21 of the flavonoids are linked by an extended,
- 22 conjugated, π -electron system. In the case of
- 23 rutin, despite the electron donating ability of the
- 24 ether group, the rate is lower than that of
- 25 luteolin. The importance of conjugation is further
- 26 highlighted by the 7-fold diminution in rate
- 27 observed when the C-ring 2,3 bond of quercetin is
- 28 saturated (taxifolin). More difficult to explain
- 29 is the activity retained by (+)-catechin which also
- 30 lacks the 2,3 double bond. Catechin differs from
- 31 taxifolin by the absence of the C-ring carbonyl
- 32 group (and use of the single stereoisomer rather

120 1 than racemic mixture). It may be that the hydrogen of the 3-OH is in close enough proximity to the B-2 3 ring to interact and increase the ability of the 4 ring to sustain unpaired electron spin density. 5 Thus a second mechanism to enhance reactivity may operate independent of resonance stabilisation 6 7 through the 2,3 double bond. With taxifolin, 8 intra-molecular hydrogen bonding of the 3-OH to the 9 carbonyl would inhibit this mechanism and may account for the 5-fold reduction in rate compared 10 11 with catechin. 12 13 Hydroxylation at the 4' position on the B-ring (position 12 in Formula 1) was an important feature 14 15 of reactivity. Comparison of the kaempferol and 16 datiscetin rate constants demonstrated a 56-fold 17 reduction in activity on moving the hydroxyl from the 4'(position 12 in Formula 1) to the 2' position 18 19. (position 10 in Formula 1). The presence of a 2'-OH 20. (position 10 in Formula 1), however, substantially

21 increases the reactivity of a hydroxyl on the 4'

22 position (position 12 in Formula 1) as evidenced by

23 the 8-fold increase in rate which morin displays

24 relative to kaempferol. Methoxylation of the 4'-

25 position (position 12 in Formula 1) of quercetin

26 (tamarixetin) resulted in a 15-fold reduction in

27 rate suggesting that the O-H bond dissociation

28 enthalpy at the 4' position (position 12 in Formula

29 1) in quercetin is most favourable for H-atom

30 transfer.

- 1 Of the fifteen flavonoids examined, eight had rate
- 2 constants greater than that of vitamin E.
- 3 Reaction stoichiometries show that many flavonoids
- 4 can undergo multiple H-atom, or electron transfer,
- 5 steps (see Table 1). Most effective in this
- 6 respect was myricetin, in which each molecule could
- 7 reduce four molecules of the radical. The non-
- 8 integer values suggest that inter- or intra-
- 9 molecular side reactions, involving partially-
- 10 oxidised flavonoid intermediates, occur. The most
 - 11 important determinant of a high stoichiometric
 - 12 value was the presence of a catechol function on
 - 13 the B-ring. Of the fifteen compounds examined,
 - 14 eight were hydroxylated at the 3' position
 - 15 (position 11 in Formula 1) and 4' position
 - 16 (position 12 in Formula 1) and had reaction
 - 17 stoichiometries ranging from 2.8 (taxifolin) to 4.1
 - 18 (myricetin). Without this functional group, the
 - 19 highest activity achieved was 1.8 (kaempferol and
 - 20 morin). The enhanced reductive capacity afforded
 - 21 by the catechol moiety is a possible consequence of
 - 22 a two-step oxidation to the ortho quinone. Morin,
 - 23 in which the second B-ring hydroxyl group is placed
 - 24 meta to the 4'-OH (position 12 in Formula 1), and
 - 25 consequently is unable to effect quinone formation,
 - 26 has a stoichiometric value of 1.8 compared with 3.3
 - 27 for quercetin in which the second hydroxyl is
 - 28 placed ortho to the 4' position (position 12 in
 - 29 Formula 1). Activity was not a simple function of
 - 30 the number of hydroxyl groups present on the B- and
 - 31 C- rings. For example, datiscetin is morin with
 - 32 the 4'-OH (position 12 in Formula 1) removed, yet

1	its reaction stoichiometry is essentially the same
2	as that of morin. Rutin, which is quercetin with
3	the 3-OH replaced by an ether-linked sugar moiety,
4	retains similar activity.
5	
6	A poor correlation ($r = 0.44$) was found between the
7	kinetic and stoichiometric parameters for the
8	reduction of galvinoxyl by flavonoids. In
9	particular, datiscetin, kaempferol and morin had
10	almost identical reaction stoichiometries (ca 1.8),
11	yet the reaction rates were 22, 1243 and 10134
12	$mol^{-1} dm^3 s^{-1}$, respectively. These results
13	highlight the importance of considering reaction
14	kinetics, as well as stoichiometry, when assessing
15	antioxidant capacity. Where two, or more,
16	potential antioxidants are present, as may occur in
17	complex cellular environments, kinetic factors may
18	greatly over-ride reaction stoichiometry in
19	determining which compound will afford greatest
20	protection. Flavonoids, such as quercetin, may get
21	absorbed from the diet into tissues. Consequently,
22	kinetics and stoichiometry must both be considered
23	in assessing the relevance of plant phenolics as
24	nutritional antioxidants for disease prevention.
25	This ESR method is a useful model to determine
26	these two distinct aspects of antioxidant activity
27	in a non-aqueous environment, as may be encountered
28	in the lipid phase of cells. The galvinoxyl
29	radical is insufficiently oxidising to
30	indiscriminately abstract H-atoms from a wide range
31	of substrates. Therefore, reactions are only
32	likely to be significant with good H-donors, i.e.

1	compounds which may fulfil an antioxidant fole
2	within a biological context.
3	
4	Example 18
5	
6	Inhibition of TBARS production in rat liver
7	microsomes from vitamin E-deficient rats by pre-
8	incubation with target antioxidant and related
9	compounds.
LO	
L1	Background
L2	
L3	Microsomes are subcellular fractions containing
4	membrane fragments. In vitamin E-deficient rats,
L 5	microsomes are especially prone to oxidative free
L6	radical damage. This can be quantified in terms of
L7	the production of thiobarbituric acid reactive
18	substances (TBARS) which result from radical-
.9	mediated destruction of the polyunsaturated fatty
20	acid constituents. Consequently, this is a useful
21	biological model to determine the efficacy of
22	phytochemicals as antioxidant membrane protectants.
23	Vitamin E-deficient microsomal suspensions were
24	incubated for 30 minutes with one of myricetin,
25	sample A, sample B, sample C (as shown below) or d-
6	alpha-tocopherol, or with a compound 9c, 9d, 9e,
27	9e*, 9f, 9g, 9g*, 9h, 9i* or 9j (prepared as
8	described above in Examples 1 to 10).
9	

1

2

3

Control C

4 5

6

ОН OH OH Control B ÓН

Control D

1

3 The microsomal suspension was then added to

4 solutions containing Fe(II)-ADP/ ascorbate to

5 initiate free radical-mediated oxidation and

6 incubated for a further 0, 5, 10, 15 or 20 minutes.

7 TBARS production was then measured by HPLC.

8

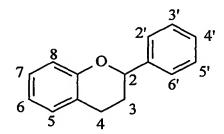
9 In all the following examples and discussions, we

10 will use the traditional numbering scheme for

11 flavonoids rather than that defined in Formula 1

12 above. The traditional numbering is as shown

13 below:



14 Results

15

16 In the absence of antioxidant protection (-E),

17 TBARS production increases with time. Myricetin

18 (M), although a potent antioxidant in chemical

19 systems affords almost no protection. Control B,

20 in which the two hydroxyls of myricetin have been

21 removed to increase lipophilicity, is very soluble

1	in octanol, and we have shown by ESR that it
2	retains potent antioxidant activity. However, it
3	does not give rise to significant membrane
4	protective effects. Replacing the B ring hydroxy
5	groups with methoxy produces a non-protective
6	compound which has a lack of antioxidant activity
7	in the ESR chemical medical system. Control E,
8	which comprises an unbranched alkyl chain linked to
9	the A-ring via oxygen and with a C_{12} alkyl chain
10	length, shows efficacy in the initial stages of
11	microsomal oxidation. However, the protection is
12	lost after 20 minutes. The target compounds
13	according to the invention suppress oxidative
14	damage throughout the 20 minute period and are
15	comparable in effectiveness to $dlpha$ -tocopherol ($lpha$).
16	
17	Table 2 below gives the TBARs data obtained for
18	compounds of varying chain length after 20 minutes
19	incubation and nomalised to a tocopherol reading of
20	20. The higher the reading the lower the
21	protection provided. The TBARS data for membrane
22	protection versus compound are presented as bar
23	graphs in Fig. 2a and Fig. 2b. The same TBARS data
24	for membrane protection plotted against compound
25	lipophilicity are presented as scatter plots in
26	Fig. 3a and Fig. 3b, respectively.
27	
28	Table 3 summarises the TBARs data obtained after 20
29	minutes incubation and normalised to a tocopherol
30	reading of 20, for compounds having different head
31	groups and chain substitution sites.
32	

- 1 The data in Fig. 2a shows that for a given head
- 2 group and position of attachment of the chain, cell
- 3 membrane protection depends strongly on the chain
- 4 length. The optimum chain length for a chain
- 5 attached at the 7-position is in the range C6 to
- 6 C12. The data in Fig. 3a shows that for a given
- 7 head group and position of attachment of the chain,
- 8 cell membrane protection depends strongly on the
- 9 lipophilicity as represented by calculated ClogP
- 10 values. For compounds 9 bearing a chain attached
- 11 to the 7-position good membrane protection is
- 12 afforded by compounds with ClogP values in the
- 13 range 4 to 10 (the compound with a ClogP value of
- 14 12 is α -d-tocopherol). The data in Figs. 2b and 3b
- 15 show the effect of varying the site at which the
- 16 chain is attached, of varying the head group and of
- 17 varying the nature of the atom linking the chain to
- 18 the head group. Compounds 9g, 11g, and 12 have the
- 19 same head group and almost identical
- 20 lipophilicities (ClogP values) but different
- 21 membrane protecting properties. Thus, we argue
- 22 that there is an orientation effect that means that
- 23 there is an optimum chain length for a particular
- 24 site of attachment of the chain to a particular
- 25 head group. Compounds 9g, 13g and 15g have the
- 26 same chain length and site of attachment of the
- 27 chain. They also have the same number of hydroxyl
- 28 groups attached to the B and C rings. It is clear
- 29 that the substitution pattern on the B-ring affects
- 30 cell membrane protection. In particular a
- 31 3,3',4',5'-tetrahydroxy-flavone head group as in
- 32 compound 9g and a 3,2',4',5'-tetrahydroxy-flavone

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- 1 head group as in compound 13g give good membrane
- 2 protection. The poor membrane protection exhibited
- 3 by compound 15g may be the result of poor
- 4 orientation as this may be affected by the head
- 5 group. Comparing the data for compound Control E
- 6 and compound 9h shows that when the chain is
- 7 attached to the head group by an oxygen atom rather
- 8 than a carbon atom, membrane protection is less.
- 9 This may also be an orientation effect.

- 11 The length of the R_A chain also appears to have a
- 12 major impact on activity (see compounds 9j, 9h, 9g
- 13 and 9d). The order of activity is $C_{18} \approx C_2 < C_{12} < C_{10}$.
- 14 This is also reflected in the two branched chain
- 15 compounds (9i* and 9g*), where the compound having
- 16 C₈ backbone has significantly higher inhibiting
- 17 effects.

TABLE 1.										
					Saps	Substitution	n Pattern	rn		
Compound	. K	Reaction	6	4	co	7	2,	3,	4,	ŝ
		Stoichiometry					1			
Catechin	1574±79	2.96±0.01	HO-H-	-H,-H.	Họ-	Ю. ,	·	НО-	田0-	
Taxifolin	337±32	2.82±0.05	но-'н-	P	Ho-	НО-		НО-	но-	
Hesperitin	6±0.5	0.20±0.02	H-'H-	Q	HO-	НО-		НО-	-OMe	
Apigenin	5±0.5	0.04±0.02	H-	0=	HO-	H0-	1 4 4 6 6 6 7 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8		HO-	
Luteolin	1212±45	3.24±0.01	H.	0=	-OH	HO-		но-	НО -	
Galangin	18±1	1.01±0.03	HO-	Q	HO-	НО-				
Fisetin	1623±199	3.68±0.03	Ho-	Q		НО-		но-	НО-	
Kaempferol	1243±99	1.84±0.01	HO-	ဝူ	НО-	НО-			-ОН	
Ouercetin	2383±258	3.27±0.04	HO	9	HO-	Hộ-		Họ	но-	
Tamarixetin	165±20	1.14±0.03	HO-	9	HO.	H0-		HO-	-OMe	
Rutin	670±41	3.18±0.01	-ORut*	Q	но-	HO-		Но-	но-	
Myricetin ,	14463±1767	4.08±0.01	HO-	ဝူ	HO.	HO-		Н0-	но-	HO-
Tri-Ome-			_		. !			9,00	O.	-OMe
Myricetin	74±14	1.06±0.02	ਲ -	ဝူ	HO-	-OH		-Owie	2010	
Datiscetin	22-42	1.74±0.02	Ę	ဝူ					1	
Morin	10134±459	1.83±0.01	Ю	ဝူ	HO-	но-	но-		В О-	:
Vitamin E	524±48	2.14±0.12			ĦĢ-	но-	Ю-			
			-	,				i		

Second order rate constants (k2) and reaction stoichiometries for the reduciton of galvinoxyl radical by flavonoids and vitamin E. *Rutin is quercetin-3-rutinoside. The compounds above the dotted line are based on the 2-H flavan system, while those below are Δ-2-flavan-4-ones.

	m,	da-toc	da-toc myricetin Control Control 9c A B	Control A	Control		p ₆	96	*e6	J 6	6	*g	3 46	*!6	j
Mean	182.783	19.9996	Mean 182.783 19.9996 147.63062 158.348 236.525 117.461 121.743 65.5291 112.546 46.1879	2 158.348	236.525	117.461	121.743	65.5291	112.546	46.1879	21.6889	21.6889 19.113 62.1021		. 32.9769	107.849
SEM	8.60267	0.86378	8.60267 0.86378 6.6099635 3.91252	5 3.91252		9.51397	9.01775	9.51397 9.01775 10.0664 14.2328 9.97687	14.2328	9.97687	0.51033	0.51033 1.76185 12.6367		9.48967	11.2272
ClogP		12.048	0.637	0.378	0.956	1.984	3.042	4.1	3.97	5.158	6.216	5.956	7.274	8.471	10.448
rable	φ M														
	щ	da	da-toc m	myricetin	Control B Control C Control D 99	Control	C Contro	ol D 99	క	Control E 11g		12	139	14	15g
Mean	182.7825		19.99965 1	147.6306	238.5249 186.6221 172.0899 21.68894 206.0328	186.622	1 172.06	399 21.6	3894 20	6.0328	81.81866	53.98257 20.1401	20.1401	104.4307	114.1373
SEM	8.602673		0.863783 6	6.609964		9.076549	9 2.393682	382 0.510328	0328	-	10.90688	10.01179	3.722299	8.686171	13.81451
ClogP		- 51	12.048 0	0.637	0.956	0.456	0.456	6.216		6.767	6.216	6.136	5.716	5.187	5.716

Table 2